

Lung function and occupational exposure among nitrate fertiliser production employees

A three year follow-up study

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National Institute of
Occupational Health



UiO : **Institute of Health and Society**
University of Oslo

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Contents

Acknowledgement.....	5
Summary	7
List of publications.....	9
Selected abbreviations.....	10
Preface.....	11
Background	12
Lung function and occupational exposure	12
Exposure assessment in occupational epidemiology	13
Exposures in the fertiliser industry	16
Previous studies on lung function in the fertiliser industry	17
Aim of the thesis	19
Historical background of mineral fertiliser production.....	20
The fertiliser production process.....	22
Materials and methods	27
Study design and population	27
Study variables	27
Assessment of respiratory function.....	27
Questionnaires.....	31
Rhinometry.....	32
Exposure assessment.....	33
Statistical analysis	36
Results.....	38
Discussion	46
Methodological considerations	46
Study design	46
Selection bias and loss to follow-up.....	49

Information bias	51
Measurement errors.....	52
Confounding.....	56
Discussion of the results	57
Exposure assessment (Paper I).....	57
Lung function (Paper II and III).....	59
Rhinometry.....	65
Analysing longitudinal data with a mixed model	65
Conclusions & recommendations	69
Ethical considerations	70
References	71
Appendices	84
Appendix I <i>Information letter 2007</i>	85
Appendix II <i>Information letter 2010</i>	88
Appendix III <i>Consent form, 2007 and 2010</i>	91
Appendix IV <i>Respiratory symptoms questionnaire, 2007 and 2010</i>	92
Appendix V <i>Work exposure questionnaire, 2010</i>	93
Appendix VI <i>Short overview of prevalence and incidence of COPD and the development of standardisation</i>	95
Appendix VII <i>Lung diffusing capacity</i>	98

Paper I, II and III

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Summary

Aim

The aim of this longitudinal epidemiological study was to investigate possible associations between occupational exposure, respiratory symptoms and change in lung function among employees at a mineral fertiliser production plant.

Material and methods

Lung function indices (forced vital capacity (FVC), the forced expiratory volume in 1 second (FEV₁) and lung diffusing capacity (DL_{CO})) were measured in 2007 and 2010 among employees at a fertiliser production plant. In 2007, 349 persons participated (86% of those eligible). Of the 283 participants remaining at work three years later, 6% did not participate in the second phase of lung function measurement. In addition to those participating in 2007, 34 additional employees participated in 2010, for a total of 383 participants. The employees consented to spirometry test and diffusing capacity test and answered a respiratory symptoms questionnaire during each testing session. In 2007, rhinometry was performed at the same time as the lung function testing. In 2010, the subjects at the plant answered a questionnaire on work history with an emphasis on the three-year follow-up period. The employees were classified in job groups by production department according to their principal affiliation during follow-up. Study participants tested only once were grouped in the department they served on the day of lung function testing. Employees in the administration or working in average less than 2 hours/week in the production were assigned to the job-group “Other”.

The exposure assessment was performed in 2007-08 in all the departments at the plant; ammonia, nitric acid, compound fertiliser, and calcium nitrate departments, as well as a shipping area. A total of 178 inhalable and 179 thoracic personal aerosol mass fraction samples were collected from randomly chosen workers (N=141), whereof 23% of the workers participated more than once. Masses of inhalable and thoracic aerosol fractions were measured gravimetrically. Water-soluble and water-insoluble aerosol fractions were analysed for the major constituents, Ca, K, Mg, and P. Concentrations of F⁻, NO₂⁻, NO₃⁻, PO₄³⁻ and SO₄²⁻ in the water-soluble aerosol fraction and leachates from impregnated gas filter-pads were analysed. NH₃, CO, and NO₂ were measured using direct-reading electrochemical sensors.

Summary

In addition, a sub study on exposure assessment using video exposure monitoring strategy was conducted during a week in May 2009 to identify short-term peak episodes.

Results

An adjusted, statistically significant decline in FEV₁ of 18 mL/year during the follow-up was found for the total group, but no significant decline in FVC. The workers in the nitric acid department had a statistically significant decline in FEV₁, but the absolute decline was of the same magnitude as for those in the Ammonia and Compound fertiliser A departments. DL_{CO} showed a statistically significant decline of 0.068 mmol/min/kPa/year for the total group. The prevalence of selected self-reported respiratory symptoms; morning cough, cough with phlegm, cough with phlegm >3 months/yr, and wheezing, varied between 6.5 to 26.2%, with only morning cough showing a statistical significant increase from 8.0% in 2007 to 13.7% in 2010. No association was found between respiratory symptoms and the decline in lung function indices, and borderline significant correlation was found between nasal patency and FEV₁% predicted. The median inhalable and thoracic aerosol mass concentration exposure levels were 1.1 mg/m³ (min-max: <0.93 - 45) and 0.21 mg/m³ (min-max: <0.085 - 11), respectively. The highest median aerosol mass concentrations were found in the compound fertiliser departments with median inhalable mass air concentration of 3.0 mg/m³ in Compound fertiliser C and median thoracic mass air concentration of 0.78 mg/m³ in Compound fertiliser A. The median air concentrations of CO, NH₃, and NO₂ in all departments were predominantly below the limit of detection (2 ppm, 3 ppm, 0.2 ppm, respectively). However, some short-term peak episodes of NH₃ and NO₂ were detected, e.g. when performing tasks like cleaning and sampling for quality control.

Conclusion

An observed adjusted decline in lung function indices was found in this three-year follow-up of workers at a nitrate fertiliser plant. The prevalence of morning cough increased in the follow-up period, but no association between respiratory symptoms and decline in lung function indices was found. A borderline correlation was found between nasal patency and FEV₁% predicted. The exposure levels for aerosols and gases were generally low with many measurements below the limit of detection. No plausible exposure related explanation for the overall lung function decline during follow-up was found.

List of publications

This thesis is based on following publications, which will be referred to in the text by their Roman numerals:

Paper I

Kristin H Hovland, Yngvar Thomassen, Nils Petter Skaugset, Knut Skyberg, Marit Skogstad, Berit Bakke:

Characterisation of occupational exposure to air contaminants in a nitrate fertiliser production plant

Journal of Environmental Monitoring (now Environmental Science: Processes & Impacts) 2012;14:2092-9

Paper II

Kristin H Hovland, Marit Skogstad, Berit Bakke, Øivind Skare, Knut Skyberg:

Longitudinal lung function decline among workers in a nitrate fertiliser production plant

International Journal of Occupational and Environmental Health, 2013;19;119-26

Paper III

Kristin H Hovland, Marit Skogstad, Berit Bakke, Øivind Skare, Knut Skyberg:

Longitudinal decline in pulmonary diffusing capacity among nitrate fertiliser workers

Occupational Medicine, first published online February 10, 2014

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Selected abbreviations

AAT	α -1-antitrypsin
ATS	American Thoracic Society
ACGIH	American Conference of Governmental Industrial Hygienists
AM	Arithmetic mean
ANOVA	Analysis of variance
BTS	British Thoracic Society
CN	Calcium Nitrate
COPD	Chronic obstructive pulmonary disease
DL _{CO}	Diffusing capacity of the lung for carbon monoxide
ECRHS	European Community Respiratory Health Survey
ECSC	European Coal and Steel Community
ERS	European Respiratory Society
FEV ₁	The forced expiratory volume in 1 second
FVC	Forced vital capacity
GSD	Geometric standard deviation
GM	Geometric mean
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
ISO	International Organization for Standardization
IUATLD	The International Union Against Tuberculosis and Lung Diseases
IVC	Inspiratory vital capacity
LLN	Lower Limit of Normal
LOD	Limit of Detection
MAR	Missing at random
MCA	Minimum cross-sectional area
MRC	Medical Research Council
NHLBI	The National Heart, Lung, and Blood Institute
NHO	Confederation of Norwegian Enterprises
NIOH	National Institute of Occupational Health
NPK	Compound fertiliser (Nitrogen, Phosphorus and Potassium)
PAF	Population-attributable factor
PIMEX	Picture Mix Exposure (video exposure monitoring)
SD	Standard deviation
SEG	Similar exposed group
SPSS	Statistical Package for the Social Sciences
TLco	Transfer factor of the lung for carbon monoxide
VEM	Video exposure monitor = PIMEX
WHO	World Health Organization

Preface

Employees in the fertiliser production industry might be exposed to aerosols from raw material and final products, acid aerosols, and various gases such as nitrogen dioxide and ammonia. The workers regularly receive health surveillance, including spirometry tests, at an occupational health service.

This study was initiated after the occupational health service at Yara Porsgrunn, in a cross-sectional survey based on the health surveillance measurements, observed a higher prevalence of chronic obstructive pulmonary disease (COPD) (cut-off $FEV_1/FVC < 0.7$) among the workers in the fertiliser production areas compared to an internal control group; 9.5% versus 2%, respectively, at the beginning of this century (T. Grimstad, MD, personal communication). The occupational health service hypothesised that the findings were associated with air pollutants in the work environment. No detailed information on the exposure levels among workers in the production facilities was obtained in the company study.

The company, as a consequence of aforementioned results, decided to further investigate possible associations between exposure and decline in lung function. Yara Porsgrunn requested the National Institute of Occupational Health to conduct a longitudinal study. The four-year study reported here was initiated in 2006 and included a prospective exposure assessment study during the three-year follow-up of lung function.



Photo. Mineral fertiliser plant under study. © Yara ASA

Background

Lung function and occupational exposure

Occupation was not considered an independent cause of chronic airflow limitation before the 1980ies (Becklake 1985). As recently as in 2010 Sigsgaard *et al* stated in an editorial; “*Data on COPD related to occupation are scarce, since the only recognised risk factor for COPD, until very recent years, has been smoking*” (Sigsgaard *et al.* 2010). Obstructive pulmonary disease encompasses several respiratory diseases including asthma and COPD. The aim was to study the lung function decline during follow-up, as an adjusted decline may indicate an increased risk of developing COPD.

Although tobacco smoking is considered the major risk factor for developing COPD, it is now well accepted that the population-attributable fraction (PAF) for the workplace contribution is approximately 15-20% (Eisner *et al.* 2010, Blanc *et al.* 2007, Korn *et al.* 1987, Balmes 2005), although PAF as high as approximately 30% has been found among workers self-reporting exposure to gas, vapours, fumes, and aerosols (Blanc *et al.* 2009) and among never-smokers (Hnizdo *et al.* 2002), and as high as 50% among never-smoking Swedish construction workers (Bergdahl *et al.* 2004). In a Norwegian study, an estimated increased risk of respiratory symptoms or asthma among those exposed to dust and fumes was found to be 15% (Eagan *et al.* 2002).

Because COPD is common in the population, even a small occupational contribution constitutes a challenge to public health. It has been estimated that approximately 250-300 000 persons have varying degrees of COPD in Norway (Johannessen *et al.* 2005), consequently one can estimate 40 000 occupational related cases of COPD in Norway.

Industry-specific studies have suggested occupational chronic obstructive pulmonary disease among coal-miners (Seixas *et al.* 1993), hard-rock miners (Hnizdo 1990) and industrial workers in Paris (Kauffmann *et al.* 1982). In Norway, studies among divers (Skogstad *et al.* 2008), tunnel workers (Ulvestad *et al.* 2001, Bakke, B *et al.* 2004), cement production workers (Fell *et al.* 2003, Nordby *et al.* 2011), aluminium potroom workers (Soyseth *et al.* 1997) and smelters (Johnsen *et al.* 2010) have identified an association between occupational exposure and an increased decline in lung function. Population studies, albeit not designed to study the relationship between occupational

exposure and obstructive pulmonary disease, have also shown this association (Humerfelt *et al.* 1993, Bakke, PS *et al.* 1991, Eagan *et al.* 2002).

Exposure assessment in occupational epidemiology

A major challenge in occupational epidemiology is accurate exposure assessments. Accurate assessment of exposure is essential to identify the hazards and to characterise the risks from low levels of exposure. Epidemiological studies that integrate quantitative exposure assessment are needed to provide new insights into the aetiology and mechanisms of action.

Industry-based studies can frequently obtain detailed information on exposure, e.g. measurement data or semi-quantitative (low, medium, high) data whereas population-based studies must often rely on qualitative exposure data (exposed vs. non-exposed). The industry-based studies can be retrospective or prospective. In retrospective studies, measurement data are often scarce, whereas in prospective studies, detailed information on exposure levels can be obtained.

A quantitative exposure assessment strategy design can be based on two basic approaches. One approach focuses on individual workers, whereas the other approach focuses on groups of workers. The choice of an individual or a group based exposure assessment strategy depends on the purpose of the epidemiological study. For studying short-term effects (within one day or week), it is often possible to monitor all the relevant biological exposures on the individual level if relevant sampling equipment is available. In practice, during a long-term study period of months and years it is excessively time consuming and expensive and hence impossible to measure the exposures to each employee every day. For that reason, sampling is performed in restricted periods and distributed across study subjects and the study period (Rappaport 1991). Workers should be chosen randomly and sampling should be performed on random days during the study period. Although the exposures of the individuals differ from the group average, the group average is assumed to reflect the exposure level for each worker. The error from measuring only a random sample of the workers in a group is compensated for by the increased precision from using all the measurements within the group to estimate the mean exposure (Nieuwenhuijsen 2003).

The primary aim of exposure assessment in occupational epidemiological studies is to optimise the exposure estimate to detect a possible risk. Today, risks associated with

occupational exposure are generally small and to detect a risk when there is a genuine risk requires the exposure assessment to be very refined (Nieuwenhuijsen 2003).

Quantitative measurements are preferred whenever possible.

Video exposure monitoring

Information on exposure levels or the time spent on various tasks can be used to improve exposure estimates in an epidemiological study and for identification of important determinants of exposure (Preller *et al.* 2004). This information can be useful in epidemiological studies in which peak exposures are hypothesised to influence the outcome. Video exposure monitoring (VEM, also known as PIMEX) combined with real-time monitors has been known since the mid-80s and has been used in task analyses for understanding and controlling exposure, in risk communication/motivation and for improvements in the work environment (Rosen *et al.* 2005). PIMEX is an established method that combines real-time monitoring instruments, typically for gases/vapours and dust, with video recording of the worker's activities (Rosen *et al.* 2005, Rosen *et al.* 1989). The motivation for using PIMEX is that it provides detailed information of how different exposures vary with time and the ability to connect that variation directly to the work process, identifying the causes of variability in the exposures.

Health related particle fraction

An aerosol is a colloidal dispersion of solid or liquid particles in a gas, usually air. Dust is an aerosol of solid particles with sizes ranging from sub- μm to over 100 μm . Particles may have irregular shapes and behave differently depending on the shape and densities. To predict more effectively where particles deposit in the respiratory tract, the term “aerodynamic diameter, d_{ae} ” was introduced to describe particle size (Hinds 1999). Particles that appear to have different physical sizes and shapes can have the identical aerodynamic diameter, and depending on their aerodynamic diameter the particles reach different part of the lungs (Vincent 1995).

In 1993, “Workplace atmospheres. Size fraction definitions for measurement of airborne particles.” was published by the European Committee for Standardization (European Committee for Standardization (CEN) 1993). This standard defines the health-related aerosol fractions:

Background

The inhalable fraction, which includes the thoracic and respirable fractions, is defined as the mass fraction of total airborne particles which is inhaled through the nose and/or mouth.

The thoracic fraction, which includes the respirable fraction, is defined as the mass fraction that penetrates the respiratory system beyond the larynx.

The respirable fraction is defined as the mass fraction that penetrates to the unciliated airways of the lung, known as the alveolar region, where the gas exchange takes place.

Figure 1 shows that particles with an aerodynamic diameter larger than approximately 10 μm cannot reach the alveolar region of the lung.

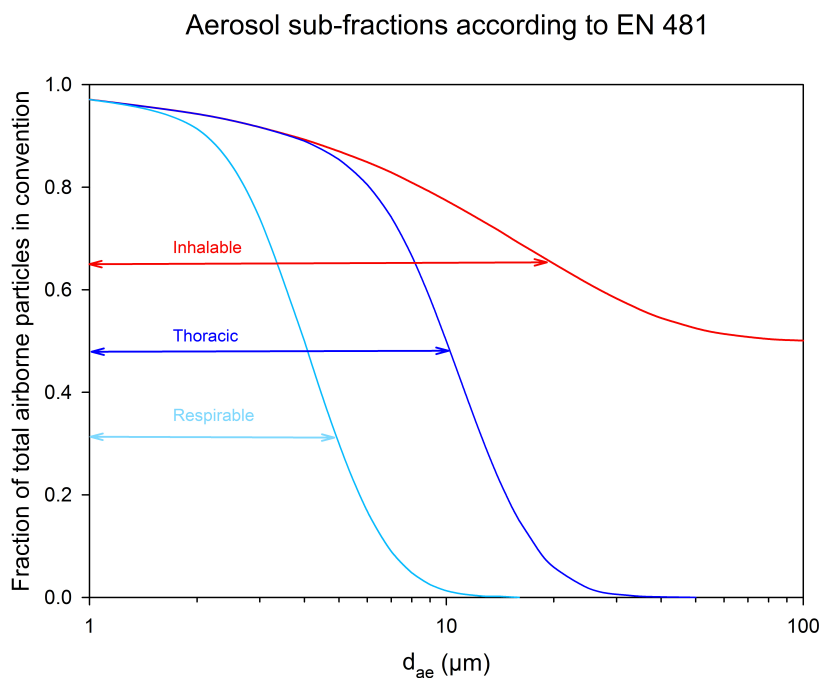


Figure 1. Overview of aerosol sub-fraction according to EN 481

Background

This standard can also be illustrated on this rudimentary drawing of the human respiratory tract (figure 2).

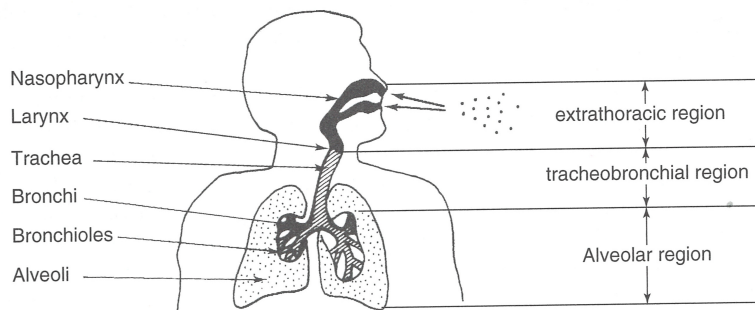


Figure 2. Human respiratory tract and aerosol sub-fractions. Reproduced with permission from Vincent, Aerosol sampling © 2007, John Wiley and Sons.

For obstructive chronic disease, the tracheobronchial fraction is thought to be the most appropriate fraction (Vincent 2005). There are no sampling devices that can measure this fraction. It can be deduced from the thoracic fraction minus the respirable fraction, but frequently the thoracic fraction is regarded the most relevant for this purpose.

Exposures in the fertiliser industry

Fertiliser production is a worldwide industry, and in the production process, workers may be exposed to aerosols, nitrous gases, ammonia, and acid aerosols.

In the fertiliser industry nitrogen oxides derives predominantly from the production of/using nitric acid. Earlier studies have shown decreased lung function and increased airway inflammation in relation to nitrogen dioxide exposure with exposures as low as 0.6-2 ppm, (Frampton *et al.* 2002, Frampton *et al.* 1991, Blomberg *et al.* 1997, Blomberg *et al.* 1999). In a study from Norway, Bakke *et al* suggested that temporary reduction in lung function might be explained by the observed peak exposures up to a maximum of 20 ppm to nitrogen dioxide (Bakke, B *et al.* 2001).

Ammonia is produced on the premises, and thereafter used in the production of nitric acid and compound fertiliser. Ammonia exposure, in the range of 25-50 ppm, has been shown to irritate the upper airways in humans (Sundblad *et al.* 2004, Ballal *et al.* 1998). No effect on dynamic lung function was found at chronic occupational exposure to low levels of ammonia (9.2 ppm) (Holness *et al.* 1989) nor 50-140 ppm (Verberk 1977).

Rahman *et al* found that ammonia exposure was associated with respiratory symptoms and an acute decline in lung function (Rahman *et al.* 2007). The acute effects of high concentrations of ammonia may be fatal or lead to long-term impairment of respiratory symptoms (de la Hoz *et al.* 1996, Leduc *et al.* 1992, Flury *et al.* 1983).

There are few studies on pulmonary effects of occupational exposure to the inorganic acids, and none of them reports any clear association (Gamble *et al.* 1984, Arnoldo *et al.* 2004, Koenig *et al.* 1994, Aris *et al.* 1993).

Population studies from several countries have shown a higher prevalence of obstructive pulmonary disease among those reporting occupational exposure to dust and gases (Bakke, PS *et al.* 1991, Korn *et al.* 1987) Bergdahl *et al* found that occupational exposure increases mortality due to chronic obstructive pulmonary disease among construction workers (Bergdahl *et al.* 2004), and Kauffman *et al* found that the decline in FEV₁ was significantly related to inhalation of mineral dust (Kauffmann *et al.* 1982).

Previous studies on lung function in the fertiliser industry

A literature search resulted in six papers which contained data on lung function among fertiliser workers. Some of the cross-sectional and cross-shift studies from various countries have shown reduced lung function and/or increased level of respiratory symptoms among workers in the fertiliser industry (Renke *et al.* 1987, Bhat *et al.* 1993, Geetha *et al.* 2001, Ballal *et al.* 1998, Ali *et al.* 2001, Rahman *et al.* 2007).

Table 1 gives an overview of the studies. Five studies were cross-sectional studies, and one was a short-term follow-up study. A major weakness of many of these studies was limited exposure data.

A limited number of epidemiological studies on cancer among fertiliser production workers have been published in the Scandinavian countries. Studies on possible associations between airborne nitrate and cancer have not shown an excess of gastric or lung cancer (Rafnsson *et al.* 1990, Hagmar *et al.* 1991, Fandrem *et al.* 1993). One of the studies was performed on the same site as ours and provides information on earlier exposure at this plant (Fandrem *et al.* 1993).

Background

Table 1. Overview of epidemiological studies of lung function in fertiliser enterprises

Author	Country	Year	Number of		Study design	Adjustments for		Exposure assessment ^a	Outcome variables ^b	Conclusion ^c
			exposed	controls		age	smoking			
Renke W <i>et al</i>	Poland	1987	116	13	Cross-sectional	Four age-groups	Uncertain ^d	Categorised into 3 groups dependent on duration of service	S	-
Bhat MR <i>et al</i>	India	1993	91	68	Cross-sectional	Not age-adjusted	Non-smokers only	By workplace + regrouped to exposure above or below 10 y	LFT	+
Ballal SG <i>et al</i>	Saudi Arabia	1998	161	355	Cross-sectional		Non-, ex-, and current smokers	Stationary air sampling for ammonia. Exposed categorised into two groups of below or above TLV ^e , or regrouped into ≤50 mg/m ³ .y and >50 mg/m ³ .y	S	+
Geetha B <i>et al</i>	India	2001	175	61	Cross-sectional	Three age-groups	Smokers/non-smokers	Duration of exposure	LFT	+
Ali BA <i>et al</i>	Saudi Arabia	2001	77	355	Cross-sectional	Yes	Non-, ex-, and current smokers; smoking hubble bubble	Stationary air sampling for ammonia. Exposed categorised into two groups: ≤50 mg/m ³ .y and >50 mg/m ³ .y	LFT	+
Rahman H <i>et al</i>	Bangladesh	2007	Urea plant: 64 Ammonia: 24		Cross-shift		Smokers/non-smokers	Personal air sampling for ammonia. Categorised into work place	S/LFT	+/+

^a exposure assessment used in analyses regarding lung function

^b S=respiratory symptoms; LFT=lung function test. Information on possible non-lung function tests not included in the table

^c “+” equals statistically significant difference for one or more respiratory symptoms/lung function parameters

^d Uncertain whether smoking is adjusted for

^e Threshold Limit Value

Aim of the thesis

The aim of this thesis was to investigate possible associations between occupational exposure, respiratory symptoms and change in lung function among the employees at a mineral fertiliser production plant.

The following objectives were established:

- to investigate the decline of dynamic lung function and lung diffusing capacity during a three-year follow-up among the employees at a fertiliser production plant
- to characterise the present personal exposure to aerosols and gases among the employees at a mineral fertiliser production plant
- to study any association between respiratory symptoms and decline in lung function
- to study the correlation between nasal patency and dynamic lung function

Historical background of mineral fertiliser production

How the mineral fertiliser industry began in Norway

On Friday, the 13th of February 1903, businessman Samuel Eyde and scientist Kristian Birkeland were invited for dinner by cabinet minister Gunnar Knudsen. During the dinner, Eyde told Birkeland about his studies on nitrogen and his purchase of the rights to certain waterfalls in Norway. He said: “*What I want most is the most powerful electric flame on earth.*” Birkeland replied: “*I can provide that, Mr. Eyde.*” This meeting is regarded as the beginning of the industrial fairytale of “Norsk Hydro”, formally established in 1905.

Natural fertilisers have been used since the early days of agriculture. Various materials have been used; e.g. animal manure, seashells, vegetable waste, and ashes. At the beginning of the 20th century it was assumed that these supplies would not suffice for the growing demand for fertiliser. It was known that nitrogen should be in a form that could be absorbed by plants and that nitrogen was abundant in the atmosphere. The challenge was to find a way to transform large quantities of nitrogen at a reasonable cost.

The Birkeland-Eyde process fixes atmospheric Nitrogen (N_2) into nitric acid (HNO_3) by having air blown through an electrical arc forming nitrogen monoxide (NO), which reacts with oxygen to yield nitrogen dioxide (NO_2). Nitrogen dioxide is dissolved in water to yield nitric acid. The process is extremely energy intensive. Close proximity to electric energy was required, and the first two plants were built in Notodden and Rjukan (1905-11) where hydroelectric power was available. Electro technology made rapid progress and Norsk Hydro soon wanted to build a production plant on the coast. The island, Herøya, Porsgrunn, was flat and near natural deposits of limestone and with easy access to the sea, required for transporting raw material and final products. The island was bought in 1912, before the beginning of World War I. During the war the Haber-Bosch method was developed in Germany; it was a superior method for producing ammonia by converting nitrogen and hydrogen under pressure and at high temperature using reaction catalysts. In 1927, Norsk Hydro bought the license for building ammonia-producing plants modelled on the Haber-Bosch method on Notodden and Rjukan, which meant that their product would be altered.

On January 14th, 1928 Norsk Hydro announced they had chosen Herøya, Porsgrunn, as the site of their new plant. On February 1st, 1928, general director Aubert gave a lecture in Porsgrunn about the plans. During the dinner afterwards he said; “*By the way, I forgot to say*

Historical background of mineral fertiliser production

that we start at Herøen tomorrow.” The next day, a line of people waited to get a job. On June 1st, 1929 the production began (Cartridge 2005).



Photo. Production plant site – historical photos (courtesy of Hydro).

In 1939 the director at Eidanger Salpeterfabrikk, Herøya, Tormod Gjestland, invited Dr. Eyvind Thiis-Evensen, Sr. to a meeting and asked him to work as a doctor at the factory. Dr. Thiis-Evensen started working part-time in 1940, but in 1941 the job became a full time position. The preventive medicine of today did not exist in the beginning of Norsk Hydro's history, although health workers had been employed by the company from the establishment. The occupational health service worked and prospered for many years, and at the most 17 physicians were concurrently employed. There was at one time a ward with 20 beds, and 100 persons could be treated for gas-induced injuries. Thiis-Evensen, Sr. was influential in establishing the first regional hospital department of occupational medicine in Norway, at Telemark County Hospital (St. Josephs Hospital, Porsgrunn). The majority of the studies from this period were in cancer epidemiology. The development of the occupational health service at Herøya, a significant element in the history of occupational medicine in Norway, is noteworthy as a background to this study (Thiis-Evensen, Sr 1985).

The fertiliser production process

Fertiliser products differ according to raw materials and processes. Ammonia, nitric acid, apatite and potassium salts are the primary raw materials for the production of compound fertilisers. At the current plant the major product is compound fertiliser, containing varying ratios of two or three macronutrients, nitrogen (N), phosphorus (P), and potassium (K) and varying amounts of micronutrients. For the products containing magnesium and boron, kieserite and borax are used. At the current plant, the production runs by the nitrophosphate route. The complete industrial process is performed at the site (Kongshaug 1991).

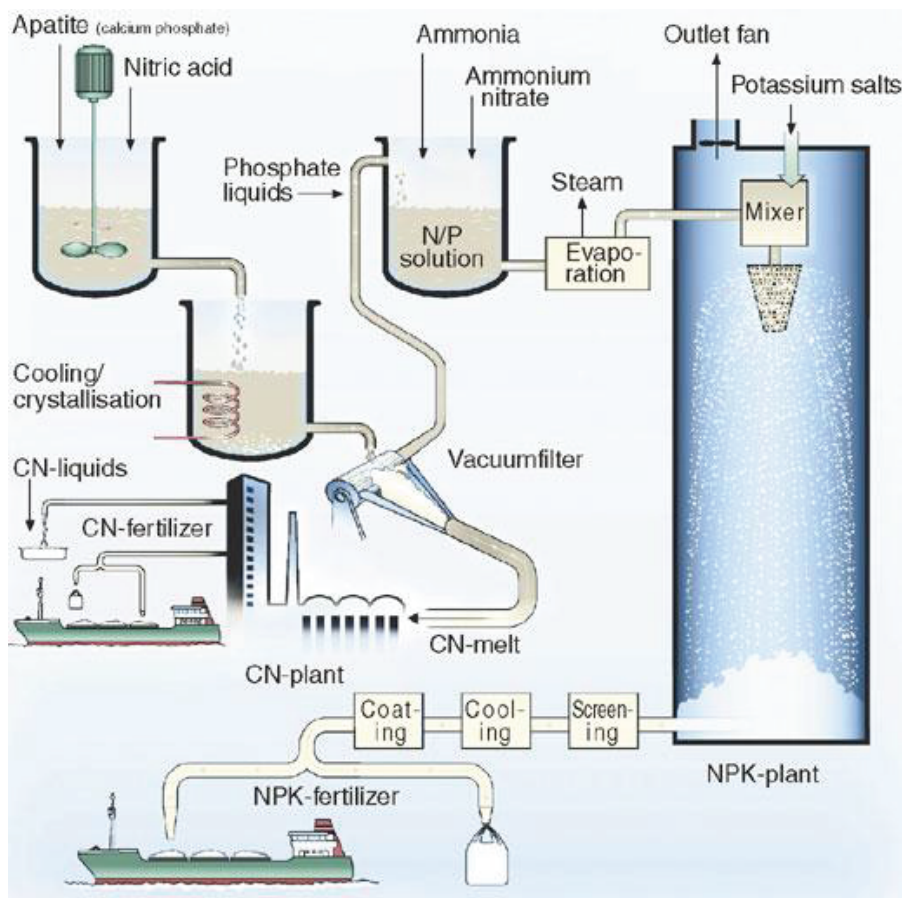


Figure 3. Illustration of production process © Yara ASA

The fertiliser production process

Principally, mineral dust, water-soluble and water-insoluble compounds, nitric acid (HNO_3), nitrogen dioxide (NO_2), nitrogen monoxide (NO), ammonia (NH_3), and hydrogen fluoride (HF) may be released into the work environment in the various departments.

In short, the process is based on the dissolution of phosphate rock in mineral acid followed by neutralisation, concentration, and granulation or prilling.

The workers in the plants work shifts, and the production units run all year. Shift-work indicates working day, afternoon or night, including weekends. The majority of employees work in one department only. In all the departments, the employees have job rotations with some days in the control room only and other days working in the production area. When working in the production area the workers usually make assigned rounds that take from 30-90 minutes. On the rounds, the workers conduct specific tasks such as quality control sampling and cleaning. Some of the tasks require more time, some are performed every day, and others at specified intervals. Table 2 provides a short overview of the production departments, possible exposures, and personal protection equipment.

The fertiliser production process

Table 2. Overview of production departments, possible exposures, and personal protection equipment

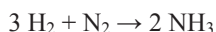
Ammonia department	Normally no exposure is expected as the production runs in closed circuits. Possible exposures may be ammonia (NH ₃) and carbon monoxide (CO) when performing check-up rounds in the production area. Respirator with dust and/or gas filter. Fresh air mask/filter mask.
Nitric acid department	Normally no exposure is expected except for when sampling as the production runs in closed circuits. Possible exposures may be ammonia and nitric oxides (NO/NO ₂) when performing check-up rounds in the production area. Respirator with dust and/or gas filter. Fresh air mask/filter mask.
Compound mineral fertiliser departments	Main exposures are ammonia, nitric acid (HNO ₃), ammonia nitrate (NH ₄ NO ₃), nitric oxides, and dust in the production areas. Respirator with dust and/or gas filter.
Calcium nitrate department	The main expected exposures are ammonia, ammonia nitrate, and nitric acid in the first part of the production (“wet part”). Dust will be the main exposure in the “dry part”, including pan granulation and checking the conveyor belts. Respirator with dust and/or gas filter.
Shipping area	Loading and unloading of raw material and final products can be dusty. Walking along the conveyor belt on check-up rounds can be dusty; the amount of dust varies with the type of product. Exhaust, mostly outdoor driving. The cranes, trucks, and dumpers all have ventilation system. Respirator with dust and/or gas filter.

The fertiliser production process

Ammonia

Ammonia is produced by the Haber–Bosch process which uses liquefied petroleum gas as the raw material. The following main steps are included in the process:

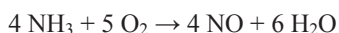
- removal of sulphur compounds
- primary and secondary reformer in which hydrogen and carbon monoxide is formed
- shift conversion to convert carbon monoxide to carbon dioxide and hydrogen
- absorption of carbon dioxide in water
- methanation, if necessary, to remove even small residual amounts of carbon monoxide and carbon dioxide
- finally the gas has the correct ratio of hydrogen and nitrogen and is compressed before the synthesis over a catalyst to ammonia



Nitric acid

Ammonia is converted to nitric acid by these main steps:

- Ammonia evaporates and the gas is mixed with heated air; the oxidation, in the presence of a platinum catalyst, produce nitric oxide



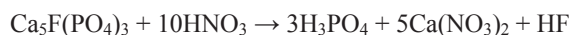
- Nitric oxide is oxidised to yield nitrogen dioxide. Nitrogen dioxide is readily absorbed in water at high pressure and low temperature, and nitric acid is formed (65%).

Compound fertiliser

Compound fertiliser contains nitrogen, phosphorus and potassium in various combinations.

The main steps in producing compound fertiliser are the following:

- Dissolution

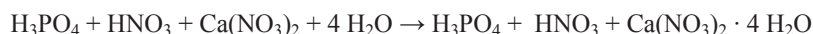


Varying amounts of nitrogen oxides (NO_x), hydrogen fluoride (HF), and carbon dioxide (CO_2) may be liberated. Urea is added at the outset to prevent the formation of NO_x .

The fertiliser production process

- Neutralisation.

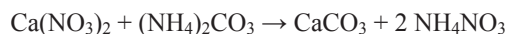
“Mother lye” (Moderlut), which now contains phosphoric acid, nitric acid, hydrofluoric acid, resolved Ca and Mg and low concentrations of contaminants, such as Fe, Al, and Si, and unresolved material (such as quartz), is cooled and calcium nitrate tetrahydrate crystallises out:



- Calcium nitrate is filtered and transferred to the calcium nitrate plant.
- The solution of phosphoric acid, nitric acid and remaining calcium nitrate, called nitrophosphoric acid, is neutralised with ammonia.
- Mixing and prilling. In the mixing process potassium/magnesium salts, sulphate and/or micro-nutrients, as specified for the product, are added. The final blend goes directly to the prill tower.
- Cooling, screening, and coating

Calcium nitrate

- The calcium nitrate crystals are dissolved in ammonium nitrate solution and treated with ammonium carbonate solution:



- The neutralised calcium nitrate melt is purified in decanter-centrifuges. Evaporation yields a higher concentration
- Pan granulation. This solidification produces a salt composition of ammonium nitrate, calcium nitrate and water.
- Cooling, screening and coating

Shipping area

The shipping area consists of locations for the unloading of raw material, storage and packing of final products, and the loading of final products. Coating of the final products is performed there, in a closed system. Contrary to work in the other departments, working in the control room in the shipping area includes checking the conveyor belts during the shift; other jobs include operating a crane, truck or dumper all day.

Materials and methods

Study design and population

This thesis is based on a longitudinal study on lung function indices, including self-reported respiratory symptoms, at a fertiliser production plant in Norway (Paper II and III). Within this study is an exposure study during follow-up (Paper I). Lung function was measured at two points, in 2007 and 2010. At baseline, nasal patency was also measured. Exposure measurements were performed over a one year period during 2007-08. A sub study on exposure assessment using video exposure monitoring, was performed during a week in May 2009. Both in 2007 and 2010, the employees answered a questionnaire on respiratory symptoms as well as smoking status (Appendix IV). In 2010, all the attendants answered a questionnaire on past work history and possible exposures, former short-term peak episodes, and use of personal protective equipment, with an emphasis on the follow-up period (Appendix V).

All plant employees were invited to participate in the study (Appendices I and II). A total of 406 persons were eligible in 2007, and 349 (86%) persons participated. Of the initial group, 283 persons remained at work in 2010, of which 263 persons participated in the follow-up; 34 employees participated in 2010 only. The total number of study participants was 383.

There were various reasons for not participating, e.g. being on sick or maternity leave, being too busy at work, being absent from work on the day of examination, or choosing not to participate. The non-participants worked at all the different departments of the plant. The main reasons for leaving work after 2007, were retirement or moving to another job.

All participants gave written informed consent on both occasions (Appendix III). The protocol was approved by the Regional Ethical Committee of South-East Norway and the Norwegian Data Inspectorate.

Study variables

Assessment of respiratory function

Spirometry

A bellow spirometer, Vitalograph 2160 (Vitalograph, Buckingham, England, using Spirotrac IV 4.32 for the data collection), was used in 2007 and 2010. The majority of

Materials and methods

employees had previously performed spirometry tests at the occupational health service, but instructions about the procedure according to the American Thoracic Society/European Respiratory Society (ATS/ERS) 2005 criteria (Miller *et al.* 2005) were given before the subjects performed the test. The Vitalograph records the volume-time curve for a period of 12 seconds on a chart, but the electronic reading of the machine records the expiratory volume for a maximum of 20 seconds. A detailed description of the spirometry test is described in Paper II. The surveys were performed at the same time of the year and by the same physician (Hovland). Reversibility testing using a beta-2-agonist was not considered feasible in this occupational setting and was not performed. Some tests not fully meeting the criteria were thought to still give valuable information (Miller *et al.* 2010, Becklake 1990) and were included after careful consideration. The spirometry test was performed on site, and the spirometer apparatus was moved among the various factories/offices. The spirometer was calibrated daily, and repeated calibration was performed if the temperature in the room rose by more than 2 degrees. When the instrument was moved, it was placed in the new position for a minimum of one hour before use (typically overnight) and calibrated before further use.

Acceptability issues and exclusion criteria for spirometry tests

The ATS/ERS criteria were followed (Miller *et al.* 2005). However, the data from some of the tests not fulfilling the criteria were included (Miller *et al.* 2010). The following list was used to categorise spirometry tests according to the quality check work. The given quality code index of each spirometry test was used to include or exclude the test during the statistical analysis.

- 0 not approved
- 1 everything OK
- 2 unsatisfactory start of expiration
- 3 the difference between the largest and the next largest $FEV_1 > 0.150$ L
- 4 the difference between the largest and the next largest FVC > 0.150 L
- 5 did not meet the plateau criterion (< 25 mL in one second)
- 6 test < 6 second (accepted on the basis of the plateau criterion)
- 7 accepted after consideration
- 8 excluded FVC (but not FEV_1)
- 9 excluded FEV_1

Materials and methods

The tests not meeting the end-of-test criterion of the plateau criterion (<25 mL exhaled in the previous second of the blow) (N=193 of 649), and/or the two largest values of FVC/FEV₁ not being within 0.150 L of each other (N=69) were included in the analysis. One spirometric result from 2007 and four results in 2010 were excluded from the study due to failure of a valid spirometry. In five cases, FVC results were not valid, although those for FEV₁ were, and here only the FVC parameter was excluded.

The single-breath lung diffusion capacity test

The workers were instructed about the entire manoeuvre of the test before starting. Information on lung diffusing capacity is in Appendix VII, and the detailed procedure regarding measurement testing of lung diffusing capacity is described in Paper III. The identical Sensor Medics Vmax 22 model (CareFusion, Ca, USA) was used on both occasions. The results are expressed in SI unit mmol/min/kPa. All the measurements were performed according to the guidelines recommended by ATS/ERS 2005 (MacIntyre *et al.* 2005) with the exception of the subjects standing instead of being seated. The technical construction of the apparatus required us to choose the standing instead of the sitting position for the subjects. All the tests were instructed by the same physician (Hovland). The gas mixture contained 0.3% CO, 0.3% methane (CH₄), 0.3% acetylene (C₂H₂), 21% oxygen, and balance nitrogen. The instrument was calibrated daily during the study, using a 3 L syringe and the calibration gas (4% CO, 16% oxygen and balance nitrogen) (CareFusion, Ca, USA). The Jones and Meade breath hold time calculation method was used (Jones *et al.*). Patient dead space volume was set to 0.150 L, and the washout volume was 0.75 L. There was no adjusting for Hb, and no corrections were made for carbon monoxide back pressure by carboxyhaemoglobin (COHb), but the smoking status and last cigarette smoked were noted.

Acceptability issues and exclusion criteria for lung diffusing capacity tests

The ATS/ERS criteria were followed (MacIntyre *et al.* 2005). The following list was used to categorise the lung diffusing capacity results according to the quality check work. The given quality code index of each diffusing capacity test was used to include or exclude the test during the statistical analysis.

- 0 not approved
- 1 everything OK
 - Inspired volume >85% of FVC within 4 sec

Materials and methods

- Two tests within 10% or 1 mmol/min/kPa
 - Breath Hold Time 10 ± 2 sec
 - expiration < 4 sec
- 2 approved after consideration
- 3 only one approved test
- 4 inspiration > 4 sec
- 5 exhalation > 4 sec
- 6 Breath Hold Time higher or lower than 10 ± 2 sec
- 7 two tests larger difference than 1 mmol/min/kPa or 10%
- 8 test $< 85\%$ of FVC
- 9 one test $< 85\%$ of FVC but DL_{CO} within 1 mmol/min/kPa or 10% of the highest value
- C modified sample collection volume vs. machine
- S smoked less than 2 hours ago
- A “Extra air”
- V IVC (inspiratory vital capacity) $> FVC$
- X did not perform DL_{CO} test, but had undergone spirometry

If "normal" expiration at the beginning, but not full exhalation < 4 sec – code 1 was used.

This method of coding all the manoeuvres yields a large variety of codes, e.g. 1: fully accepted; 1V: fully accepted, but one or both manoeuvres had $IVC > FVC$; 23: only one approved test, but included in the study; 26: breath hold time outside 10 ± 2 sec (one or both tests); 24SV: inspiration > 4 sec, smoked less than 2 hours ago, $IVC > FVC$ on one or both manoeuvres and so forth. In all the cases in which code 2 was used, whether the test should be included or not was thoroughly considered. Test quality outcomes for DL_{CO} are shown in table 3.

Table 3. Distribution of test quality outcomes for lung diffusion capacity tests

Criterion	Number of tests (%)
0	39 (7.5)
1	287 (55.5)
2	191 (36.9)

0 excluded

1 accepted according to standardisation

2 accepted after consideration

Materials and methods

Table 4 gives an overview of the participants performing lung diffusion capacity test at the two times when the surveys were performed. A higher percentage was excluded in 2007 than 2010. The primary reason is most likely that the test was new to most participants in 2007, and thereby slightly difficult to perform. The majority of the excluded tests in 2007 are because of excessively long breath hold time. A higher percentage did not participate with DL_{CO} in 2010, mainly because of smoking prior to the test or no test performed in 2007. The criterion of not smoking 2 hours prior to the test was more rigorously followed in 2010.

Table 4. Overview of participants at the two points of lung diffusing capacity testing

Year	No of tests	Excluded	Accepted	DL_{CO} test not performed (but spirometry)
2007	308	37	271	41
2010	209	2	207	92

Two hundred (39%) of the tests showed IVC above FVC on one or both trials, and only 2 persons had $IVC < 85\%$ FVC. (The criteria stated that inspiratory vital capacity should be $>85\%$ of largest vital capacity in < 4 seconds.)

Questionnaires

Respiratory symptoms

A standardised, self-administered respiratory symptom questionnaire in Norwegian; an extended version based on the British Medical Research Council questionnaire (British Medical Research Committee 1960), was used initially and at the three-year follow-up survey (Appendix IV) (Paper II and III). The questionnaire was used to obtain information regarding respiratory symptoms, some previous illnesses, allergy, asthma, airway symptoms, and smoking habits.

Work history

The individual occupational history was taken at the survey in 2010 (Paper II and III). Each participant answered a questionnaire on the work place(s) and job tasks during the follow-up, in addition to questions about former occupations and exposures (Appendix V). Occupational and non-occupational exposures known to possibly affect lung function were

Materials and methods

asked for specifically, together with information on the use of personal protection equipment (PPE).

Rhinometry

Rhinometry is a non-invasive and easy method to measure nasal patency. Acoustic signals generated in a tubular probe are sent up the nasal passageway and reflected out in such a way that the procedure can accurately map out the topography of the nasal airway. The method is fast and without adverse effects. It has been found to provide a valid result at least for the first 5-6 cm of the nasal cavity (Hilberg 2002). A standardisation of the procedure was published in 2000 (Hilberg *et al.* 2000). Acoustic rhinometry (SRE Rhin2100, Rhino Scan version 2.6, Rhino Metrics AS, Denmark) was performed in 2007 with the subject in a seated position, using a handheld sound wave tube and an anatomical nasal adapter. The following variables were recorded: the second total minimum cross sectional area (MCA2) and volume (VOL2) previous of this deflection, measured at 22-52 mm from nostril, see photo below and figure 4.



Photo. Performing rhinometry on a worker (private)

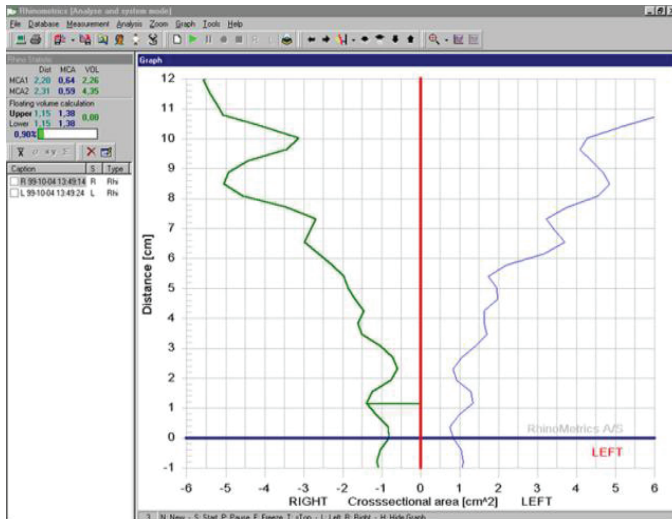


Figure 4. Example of an acoustic rhinometry profile

Exposure assessment

Sampling strategy for the epidemiological study

All the production departments at a fertiliser plant in Norway were included in the exposure assessment (Paper I). Information on the production processes and job tasks in all the departments were obtained during several walk-through surveys at the plant before the exposure measurements were initiated. Included in these visits were interviews with workers and management.

The selection of workers and day of the week were chosen randomly. The objective was that each participant carried sampling equipment for a minimum of two days. All the samples were collected outside personal protective respirators. The workers on duty in the control room on the day of measurement were excluded from the sampling as they are assumed to be unexposed when in the control room. This air sampling strategy makes it possible to estimate the exposure for all workers, including those not selected for participation in the exposure measurements, according to their affiliation with the groups that are subject to the measurement campaign and to assign group-based estimates of exposure to all the members of the group.

Materials and methods

The thoracic fraction was used on the assumption that the exposure to the bronchial tree may reflect the outcome of obstructive lung function changes to a higher degree than other aerosol fractions. The inhalable fraction was included to provide information on the extrathoracic fraction.

Personal air sampling methods and analyses

The inhalable aerosol fraction was collected using the IOM (SKC Ltd., Blandford Forum, Dorset, UK) personal sampler at 2 L/min and the thoracic aerosol sub-fraction was collected using a BGI GK2.69 cyclone (BGI Inc., MA, USA) at 1.6 L/min. The thoracic aerosol fraction, inorganic gases, and acid vapours were collected simultaneously by placing two 37 mm impregnated gas filter-pads (cellulose support pads) after the aerosol filter by inserting an extra ring into the standard three-part aerosol filter cassette (Millipore, MA, USA) (Paper I). The first filter-pad for collection of HNO_3 vapour and HF was impregnated with 10% (w/v) potassium hydroxide (KOH) in H_2O and dried at room-temperature for 24 hours. The second filter for the collection of NO_2 was impregnated with 25% (w/v) sodium iodide (NaI) and 10% (v/v) ethylene glycol in methanol and also dried at room-temperature for 24 hours.



Photo. Preparing for personal exposure sampling. (private)

The gases (NH_3 , NO_2 and CO) were measured using PACIII (Dräger Aktiengesellschaft, Lübeck, Germany) gas sensors. A period of 30 seconds as the logging interval was selected.

The limit of detection (LOD) for CO, NH₃ and NO₂ was 2 ppm, 3 ppm, and 0.2 ppm, respectively.

The gravimetric measurements of aerosol mass were performed for all the inhalable and thoracic filters. The chemical analyses included leaching of the water-soluble and the water-insoluble aerosol fraction. The concentrations of Ca, K, Mg, and P in the water-soluble and water-insoluble aerosol fractions were determined with inductively coupled plasma optical emission spectrometry (Perkin-Elmer, Norwalk, CT, USA) and the concentrations of F⁻, NO₂⁻, NO₃⁻, PO₄³⁻ and SO₄²⁻ in the water-soluble aerosol fraction and leachates from the impregnated gas filter-pads were determined by ion chromatography (Dionex, Sunnyvale, CA, USA). A thorough description of the analyses and quality control is given in Paper I.

Video exposure monitoring of short-term peak episodes

Based on the data collected in the exposure assessment study (Paper I), with the workers experiencing short-term peak episodes, a sub study using PIMEX was initiated to further identify the variability of the exposure.

PIMEX2008, with telemetry equipment for wireless transmission of the monitoring signal was used. Workers at the compound fertiliser departments, the calcium nitrate department and the shipping area participated during one week in May 2009. Only those working in the production area on the day of sampling were selected, and the workers were followed on their regular rounds. The measurements started just before leaving the control room and ended when the worker returned to the control room. The worker carried a direct reading aerosol spectrometer (DustTrak aerosol monitor 8520, TSI, MN, USA) and NH₃ and NO₂ gas sensors (PACIII, Dräger Aktiengesellschaft, Lübeck, Germany). One investigator carried the video camera making sure the worker was always in the picture and another investigator carried the laptop computer. The signals from the DustTrak™ were synchronised with the video during the measurements, while the monitoring signals of the gases were manually synchronised afterwards.

The participants were selected to cover as many of the work tasks as possible for that department. A total of 20 rounds were performed using PIMEX strategies. The rounds were allocated as follows; Compound Fertiliser A, two rounds; Compound Fertiliser B, six rounds; Compound Fertiliser C, eight rounds; Calcium Nitrate, two rounds; and the shipping area, two rounds.

Statistical analysis

Repeated observations were available for 69% of the employees for the spirometric data and for 55% for the gas diffusion data, and a longitudinal mixed model approach was used to study change in lung function indices among the employees from 2007 to 2010 (Papers II and III). The main objective of the thesis was to study the effect of exposures to aerosol and gases on the decline in lung function. Because many of the personal air measurements of the agents that were included in the exposure assessment were below LOD, it was not feasible to calculate quantitative exposure estimates for each worker of the cohort. In the epidemiological analyses (Paper II and III) workers were therefore assigned to a job group based on the information on where they had worked during follow-up. Information on department was obtained from company records and compared to self reports from the questionnaires. Study participants tested only once were grouped in the department they served on the day of lung function testing. The employees not working in the production area, including those who reported < 2 hours on average per week in the production areas, were assigned to the group “Other” yielding eight job-groups in the epidemiological analyses. No reference group was used studying the longitudinal data, as the subjects serve as their own controls. Adjustments were made for gender, age, height, weight, smoking status, and doctor diagnosed asthma.

The absolute effects of each job group were reported. The adjusted decline was also considered for all workers without regards to job group. Furthermore, the effect of the number of years worked at the fertiliser plant had on the change in the lung function was analysed.

The mixed model analysis use actual age at years 2007 and 2010 and not the baseline values. This means that the age related decline is estimated through age only, and also that the exposure (job group) related decline is not influenced by age. To summarize, the estimated decline in lung function for a particular job group, is the decline that exceeds what is expected due to age for a person with a particular gender, height, weight, smoking and asthma status.

A mixed model includes both fixed and random effects. Fixed effects models the systematic effects of covariates as age and gender, while random effects models the dependency structure of data. Our model takes into account the dependency of the repeated observations by adding random effects for workers. The mixed model can be represented formally as

Materials and methods

$y_{ij} = \mathbf{x}_{ij}^T \boldsymbol{\beta} + u_i + \varepsilon_{ij}$, where y_{ij} is the observed pulmonary function of person i and replication j , and \mathbf{x}_{ij}^T is a vector of regressors linking the observations to the fixed effects $\boldsymbol{\beta}$. Furthermore, u_i represents independent and identically distributed normal random effects with a mean 0 and variance σ_u^2 , while ε_{ij} are independent and identically distributed normal random variables with a mean 0 and variance σ_ε^2 . Different variance structures were compared using likelihood ratio tests, and based on these σ_ε^2 was allowed to differ for the two genders.

The self-reported symptoms were analysed by McNemar's chi-squared test with continuity correction (Paper II and III).

The reference equations of ECSC (Quanjer *et al.* 1993, Cotes *et al.* 1993) and Gulsvik (Gulsvik 1979, Gulsvik *et al.* 1992) were used for baseline characteristics. When analysing the relation between changes in FEV₁ % predicted and DL_{CO} % predicted during follow-up, the ECSC reference equations were used.

Data on possible correlation between rhinometry and FEV₁ % predicted (Quanjer *et al.* 1993) were tested using a test statistic of Pearson's correlation that follows a Student's t -distribution.

In the exposure assessment (Paper I) only workers in the production areas were included as those having control-room and administration duties on the day of measurement were assumed to be unexposed. All the production departments (ammonia, nitric acid, compound fertiliser (3 departments), and calcium nitrate) and the shipping area were included. The exposure data (Paper I) were found to be best described by lognormal distributions. The standard measures of central tendency and distributions by AM, geometric mean (GM), and geometric standard deviation (GSD) was calculated using the maximum likelihood estimation, since many observations were below the limit of detection. The within- and between-worker variances were calculated using a mixed effect model. The significance of the differences in exposure levels among the departments was evaluated using ANOVA analysis with Bonferroni correction for multiple comparisons.

Linear mixed models and maximum likelihood models were analysed in R (<http://www.r-project.org>) and all other data analyses were performed with R or SPSS v 15.0 for Windows (SPSS, Chicago, Illinois, USA).

Results

Lung function indices

For the total group, there was an adjusted decrease of FEV₁ of 18 mL/yr ($p<0.001$), but no statistically significant decrease of FVC during the follow-up period (Paper II). This finding provides an estimate of the lung function changes not explained by gender, age, height, weight, smoking status, and doctor-diagnosed asthma. Studying the various job groups a statistically significant annual decrease in FVC (48 mL/yr, $p=0.0023$) and in FEV₁ (33 mL/yr, $p=0.012$) was found among the workers in the nitric acid job group. The adjusted annual change in FEV₁ varied between -33 to 11 mL per year among the job groups. The subjects in one job group, compound fertiliser B, had a statistically significant increase in FVC.

Regarding DL_{CO}, an adjusted, statistically significant decline of 0.068 mmol/min/kPa/year ($p<0.01$) was found for the entire group during the three-year follow-up (Paper III). The change in DL_{CO} varied from -0.15 to 0.12 mmol/kPa/min between the job groups. Only the job group “Other” showed a statistically significant decline in DL_{CO} ($p=0.004$). In a sub-analysis, excluding those who had smoked within 2 hours prior to testing in 2007 because of the stricter regulation of this criterion in 2010, did not change the results significantly (results not shown).

At baseline a highly significant, but weak, correlation between the percent predicted DL_{CO} and the percent predicted FEV₁ was found ($r=0.25$, $p<0.0001$). No correlation between change in FEV₁ % predicted and change in DL_{CO} % predicted during follow-up was established (results not shown).

Respiratory symptoms

No statistical significant association between selected self-reported lung symptoms; morning cough, cough with phlegm, cough with phlegm more than three months/year, and wheezing, and decline in lung function was found (Paper II and III). Studying the change from 2007 to 2010, a statistical significant increase in the prevalence of “morning cough” from 8.0% to 13.6% was observed ($p<0.01$). None of the other symptoms studied showed statistically significant changes (Paper II).

Results

In Paper II it is shown in Table 1 that smokers had lower FVC percent predicted and FEV₁ percent predicted than non-smokers at baseline. Looking at percent predicted by symptoms at baseline a similar trend is seen, with those reporting selected symptoms having a lower percent predicted of both FVC and FEV₁ than those not reporting symptoms, as shown in table 5.

Table 5. Dynamic lung function in percent predicted¹ at baseline by different symptoms and gender

	All	No symptoms	Wheezing	Morning cough	Daily cough w/phlegm	Cough w/phlegm >3 months/yr
	%pred(N)	%pred(N)	%pred(N)	%pred(N)	%pred(N)	%pred(N)
FVC male	99 (308)	102 (216)	93 (78)	91 (29)	92 (24)	94 (25)
FEV ₁ male	93 (311)	96 (218)	84 (79)	79 (29)	81 (24)	83 (25)
FVC female	112 (33)	112 (26)	110 (5)	0	112 (1)	110 (2)
FEV ₁ female	103 (33)	104 (26)	95 (5)	0	111 (1)	108 (2)

¹ ECSC reference equation

Rhinometry

In 2007, rhinometry was performed before the lung function testing (Hovland 2008). No congestion nasal spray was used because of possible interaction with lung function testing. The nasal patency was compared to dynamic lung function, and a borderline significance was found on correlation between VOL2 and FEV₁ % predicted using ECSC reference equation (Quanjer *et al.* 1993) (p=0.047) but no significant results were obtained using Gulsvik reference equations (p=0.074) (Gulsvik 1979) (figure 5).

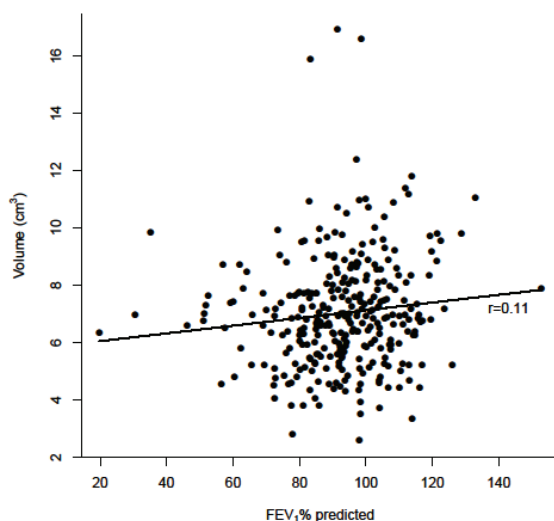


Figure 5. Correlation between rhinometry volume (VOL2) and FEV₁%predicted (ECSC reference equation)

Exposure assessment

In total, 178 inhalable and 179 thoracic personal aerosol mass fraction samples were collected from randomly chosen workers (N=141), on random days, from all the production departments; three compound fertiliser departments, a calcium nitrate fertiliser production department, nitric acid- and ammonia-production departments, and a shipping department (Paper I). The sampling time varied between 195-455 minutes (the arithmetic mean (AM) = 365 minutes).

The median inhalable and thoracic aerosol mass concentrations were 1.1 mg/m³ (min-max: <0.93 - 45) and 0.21 mg/m³ (min-max: <0.085 - 11), respectively. Studying the job groups, workers at the Compound Fertiliser departments B and C were exposed to significantly higher inhalable aerosol mass air concentrations compared to the other departments (p<0.05) except the Compound Fertiliser department A. The difference between the Compound Fertiliser department C and the Calcium Nitrate department was slightly above the significance level. The workers at Compound Fertiliser department A had significantly higher thoracic aerosol mass air concentrations compared to the other departments (p<0.05), except for Compound Fertiliser departments B and C.

Results

Figure 6 and Figure 7 shows box-plots of the inhalable and thoracic aerosol mass air concentrations for the various departments.

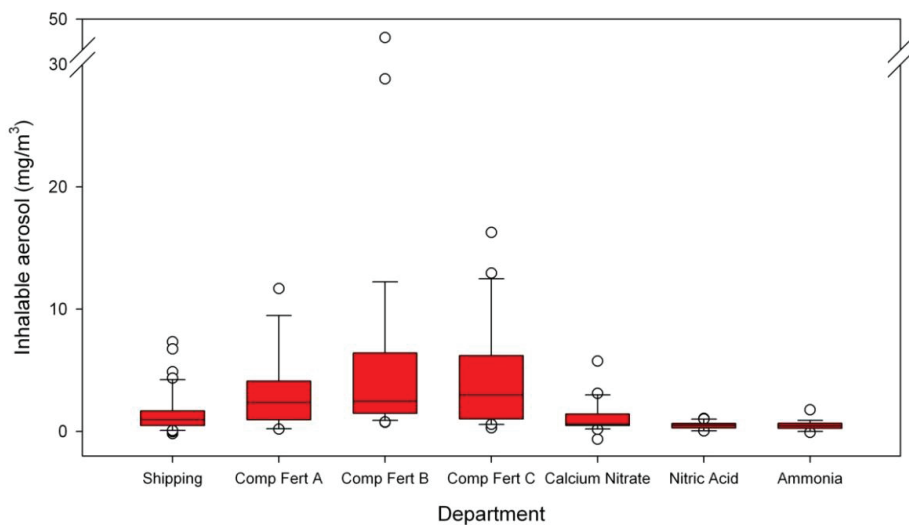


Figure 6. Inhalable aerosol mass air concentration for the departments

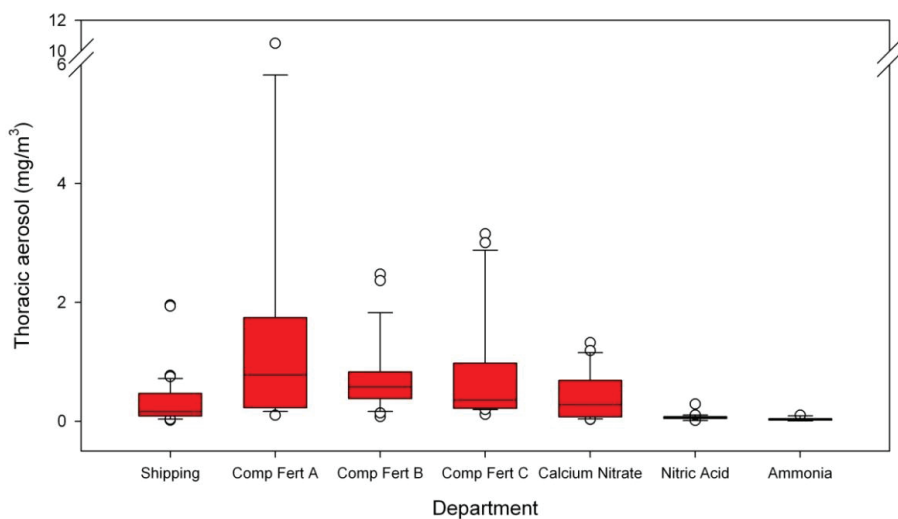


Figure 7. Thoracic aerosol mass air concentration for the departments

The measurements indicate that the extrathoracic aerosol fraction of the aerosol compared to the thoracic fraction dominated in most departments, varying from 57% to 92%. A shift

Results

towards more water-soluble species as the production goes from the raw material stage with phosphate rock towards the final fertiliser products was found.

The air concentrations of the major constituents Ca, K, Mg, and P, in the water-soluble and water-insoluble aerosol mass fractions were low. The highest median levels in the water-soluble fraction were; Ca: $85 \mu\text{g}/\text{m}^3$ in Compound fertiliser A, K: $270 \mu\text{g}/\text{m}^3$ in Compound fertiliser C, Mg: $16 \mu\text{g}/\text{m}^3$ in Compound fertiliser B, and P: $17 \mu\text{g}/\text{m}^3$ in Compound fertiliser B and C, The highest median levels in the water-insoluble fraction were; Ca: $140 \mu\text{g}/\text{m}^3$ in Compound fertiliser A, K: $7.6 \mu\text{g}/\text{m}^3$ in Compound fertiliser C, Mg: $31 \mu\text{g}/\text{m}^3$ in Compound fertiliser C, and P: $40 \mu\text{g}/\text{m}^3$ in Compound fertiliser B. All the constituents are in a neutral form, i.e. not alkaline as in the cement industry. There are no Norwegian OEL's for the constituents.

Overall, the median air concentrations of CO, NH₃, and NO₂ measured using the PACIII direct reading instrument were below the LODs (2 ppm, 3 ppm, and 0.2 ppm, respectively) for the different gases. Short-term peak episodes were observed performing specific tasks as cleaning or quality control sampling. Regarding CO, all the measurements had median values below LOD and no peaks above the Norwegian OEL (25 ppm) were measured. As for NH₃, 59 out of 60 measurements had median values <LOD and 10 measurements had max values > 25 ppm (Norwegian OEL) (logging interval 30 sec). For NO₂, all measurements had median values below LOD and 11 measurements had max values > 0.6 ppm (Norwegian OEL) (logging interval 30 sec). Quality control sampling in the nitric acid department is shown in the photo below. An overview of all the peak episodes for NH₃ and NO₂ with values above Norwegian OEL is presented in tables 6 and 7, followed by figures from two of the measurements (figures 8 and 9).



Photo. Worker performing quality control sampling in the nitric acid department

Table 6. Short-term peak events of NH₃ above Norwegian OEL of 25 ppm (personal sampling, logging time 30 sec)

Department	Compound fertiliser B						Comp fert C			Nitric acid	
	13.9.07	23.8.07	21.6.07	31.1.08	29.1.08 ^a	29.1.08	8.1.08	10.1.08	15.3.08	10.4.08	
Date	13.9.07	23.8.07	21.6.07	31.1.08	29.1.08 ^a	29.1.08	8.1.08	10.1.08	15.3.08	10.4.08	
No of peaks	3	11	1	3	1	1	1	1	1	1	
Time, peak (min)	17.5	17.5	0.5	2.5	2.5	1	16.5	1.5	0.5	0.5	
Max ppm	51	300	30	41	106	69	107	64	30	28	
Sampling time (min)	345	390	370	360	345	350	370	380	445	395	
Median ppm (total sampling)	0	2	0	0	0	-3	0	0	0	0	

^aShown in figure 8

Table 7. Short-term peak events of NO₂ above Norwegian OEL of 0.6 ppm (personal sampling, logging time 30 sec)

Department	Comp fert A			Comp fert B			Nitric acid				
	7.6.07	6.3.08	5.9.07	23.8.07	24.1.08	29.1.08	4.3.08	13.3.08	15.3.08 ^a	12.2.08	12.2.08
Date	7.6.07	6.3.08	5.9.07	23.8.07	24.1.08	29.1.08	4.3.08	13.3.08	15.3.08 ^a	12.2.08	12.2.08
No of peaks	1	8	1	6	9	4	1	1	3	3	3
Time, peak (min)	0.5	17.5	0.5	7.5	10	59	4.5	0.5	1.5	2	3
Max ppm	2	63	0.8	11.3	1.7	39.8	1.7	0.7	1.4	1.2	1.9
Sampling time (min)	360	425	355	405	320	350	365	385	445	360	365
Median ppm (total sampling)	0	0	0	0	0	0	0	0	0	0	0

^aShown in figure 9

Results

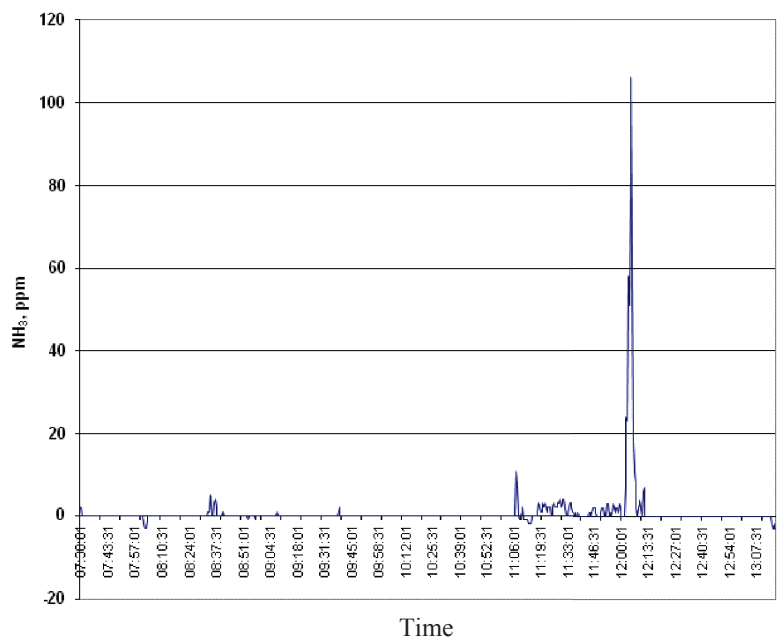


Figure 8. Direct read measurement of ammonia concentrations in Compound fertiliser B dept

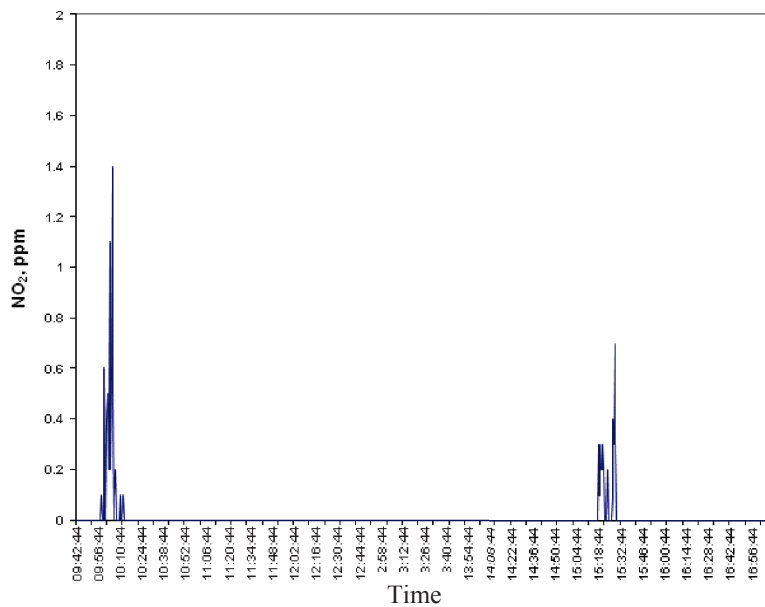


Figure 9. Direct read measurement of nitrogen dioxide concentrations in the Nitric acid dept

Video exposure monitoring of short-term peak episodes

The sub study using PIMEX confirmed the results in the exposure assessment study (Paper I) with short-term peak episodes when performing certain tasks like quality control sampling, cleaning, or inspections, and the specific tasks with short-term peak episodes were identified. Although time weighted averages of most exposures were legally acceptable, the video demonstrated high transient personal dust and gas exposure. The information could be used to assist in the reduction of personal exposures in the selected departments.

Information from such videotapes could be used to develop checklists of determinants that may affect exposure and to correlate behaviour and exposure level. Furthermore, this method could be used to develop questionnaires for epidemiological studies. However, for the latter purpose the number of representative measurements must be sufficient. The identification of behaviour-related factors in epidemiological studies may explain variation in disease risk of individuals.

The results were presented to the involved worker and foreman right after the round using PIMEX.



Photo. Video exposure monitoring in a department

Discussion

This thesis encompasses a three-year prospective cohort study on lung function including self-reported respiratory symptoms, as well as an exposure assessment study performed over one year during the follow-up time, among employees at a fertiliser production plant in Norway. The exposure assessment is accounted for in Paper I. The results on dynamic lung function (FVC and FEV₁) and respiratory symptoms are presented in Paper II and those on lung diffusing capacity (DL_{CO}) and respiratory symptoms in Paper III.

Methodological considerations

Study design

A major advantage of a longitudinal study, as opposed to a cross-sectional study, is the possibility of examining the effects of exposure on changes in the health outcome with greater accuracy since the individuals serves as their own controls and hence between-worker variation is removed (Fitzmaurice *et al.* 2004). Furthermore, a longitudinal study is robust to baseline differences and dropout mechanisms that are missing at random (MAR). A prospective longitudinal study gives more reliable information on a possible relation between current exposures and health effects. The exposure must precede the outcome in time to describe such a possible causal relation. This relation is best suited for studies in which the health outcomes occur within a relatively short time period (Checkoway *et al.* 2004). The longitudinal design in a study thus may provide information on causation if the follow-up period is within the recommended time (Bakke, PS *et al.* 2011). Three years is, however, considered to be sufficient to detect rapid decliners. Another prerequisite is that the exposure is high enough to provoke the health outcome being studied.

The limitations of prospective cohort studies include the time consumed and expenses. The loss to follow-up and the fact that longitudinal studies are susceptible to survivor bias should be considered (Eisen *et al.* 1995, Bakke, PS *et al.* 2011). The validity of the results may be questioned if the proportion of those lost to follow-up is large, i.e. 30-40%. In cases in which there are strong reasons to believe that the dropout may be related to the unobserved outcome at the follow-up, i.e. when the dropout is not missing at random, a lower percentage of lost to follow-up subjects can also be of concern. In this study the number of lost study participants during the follow-up is considered to be acceptable (25%). It cannot be excluded that some were lost due to outcome.

Discussion

Figure 10 shows a comparison of FEV₁ % predicted for dropouts and non-dropouts by age (Quanjer *et al.* 1993). This shows that dropouts were distributed over the whole age span and with various FEV₁ % predicted values.

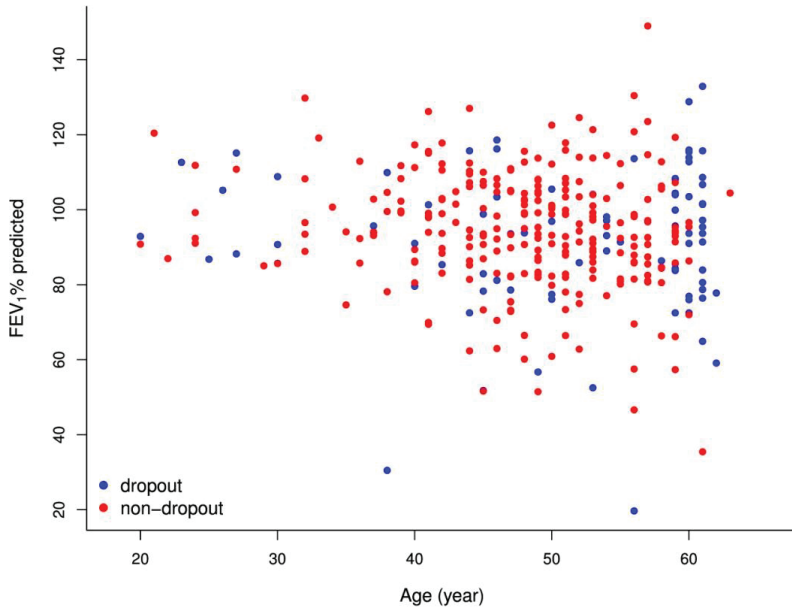


Figure 10. Baseline FEV₁ % predicted (ECSC reference equation) by dropout status and age. Dropouts, blue. Non-dropouts, red.

The two sample t-tests for inequality shows no significant difference between the baselines FVC % predicted and FEV₁ % predicted observation for dropouts and non-dropouts (table 8).

Table 8. Baseline FVC % predicted and FEV₁ % predicted for dropouts and non-dropouts

	FVC % pred ^a	FEV ₁ % pred ^a
	Mean (SD)	Mean (SD)
Dropouts (n=86)	98.6 (16.0) ^b	92.0 (19.3) ^b
Non-dropouts (n=263)	101.2 (13.7)	94.6 (15.7)

^a ECSC reference equation

^b two-sample t-test, p>0.05

Discussion

Spirometry and gas diffusion techniques are well-known and much used both in the clinic and in epidemiological studies. Measurements of FVC, FEV₁, and DL_{CO} are simple and reliable, but it is important to follow standard procedures (Miller *et al.* 2005, Miller *et al.* 2005, Pellegrino *et al.* 2005, MacIntyre *et al.* 2005). The standard procedures are made with a healthy person in mind and, e.g. subjects with pulmonary obstruction will not be able to fulfil the criteria. Kellie *et al.* showed that those with respiratory symptoms more often failed to fulfil the spirometry criteria than asymptomatic persons (Kellie *et al.* 1987). Exclusion of subjects not meeting the criteria may introduce a bias. Both the spirometric and the gas diffusion test results were quality checked by the same physician (Hovland) and some tests were included although not fully meeting the criteria (Paper II and Paper III) (Miller *et al.* 2010).

Both the questionnaires were self-reported. The employees got the questionnaires at work and a group influence, if it were filled out together, is possible. There is no indication of group influence in the replies of the employees.

Rhinometry

Nasal patency was measured using a rhinometry in 2007. The instrument is simple in use. The main reasons to measurement errors are leakage around the nostrils, too high background noise, or temperature variation (Djupestrand *et al.* 1998, Hilberg *et al.* 2000).

Sampling strategy of exposure assessment

The purpose of the sampling strategy used in this study is to provide representative exposure data, i.e. data about exposure at the group level. The exposure measurements were performed over one year (Paper I) as suggested by Rappaport *et al.* and Spengler *et al.* (Rappaport *et al.* 1995, Spengler *et al.* 1994), during the three-year period of the study. The exposure of dust and gases to each operator varies during the working day, from day to day, with the weather and seasons, and with changes in the process, the raw materials, and the tasks performed (Nieuwenhuijsen *et al.* 1995, Cherrie 1996). In practice, during a long-term study period, it is excessively time consuming and expensive and, therefore, impossible to measure the exposures to each operator every day. When assessing long-term exposure levels, sampling typically will be performed during a defined period and the mean of the exposure measurements within the group is assigned to each worker in the group.

Discussion

The strength of this study is the personal exposure measurements being performed from April 2007 till July 2008. In total, 141 workers (of 270 eligible) carried sampling equipment and 23% were monitored on more than one occasion. The workers selected for the exposure assessment were randomly chosen and all voluntarily agreed to participate. Only the workers who were scheduled to have rounds in the production area on the day of the sampling were selected and the various rounds were included throughout the sampling period. The workers participating in the exposure study were hypothesised to be representative of all the workers in the company (Paper I).

Among the first to describe a strategy with sampling performed on random workers and random days were Corn and Esmen in 1979 (Corn *et al.* 1979). Corn and Esmen introduced the concept “working zone”, where workers within the same “zones” were assumed to be similarly exposed. The “zones” were qualitatively judged based on work similarity; e.g. having the same job title/carrying out similar work, similarity to particular substances, or similarity of environmental conditions. Even though the exposure of the individual differs from the group average, the group average is assumed to reflect the exposure level for each worker. The error from measuring only a random sample of the workers in a group is compensated by the increased precision from using all the measurements within the group to estimate mean exposure.

Earlier studies have shown that exposure measurements would be more correct if the workers used personal sampling equipment (as opposed to stationary measurements), as is done in our study, even with awareness of the between-worker and within-worker variability (Rappaport 1991, Cherrie 2003). In cases in which the variability between the workers in a group is large, the variability will lower the precision of exposure-response relationships in epidemiological studies when the analysis is based on group mean exposure levels (Rappaport *et al.* 1995). The percentages of the total variance explained by department (fixed effect) for inhalable and thoracic mass fractions were 28% and 51%, respectively (Paper I). The within-worker variance was larger than the between-worker variance for the inhalable mass air concentration whereas it was equal for the thoracic mass air concentration (Paper I).

Selection bias and loss to follow-up

Selection bias occurs when the procedures used to select the subjects or factors that influence study participation lead to a distorted selection so that that the participants are not

Discussion

representative of the employees within the company (internal) or for the trade (external) with respect to exposure and outcome. In this study, only persons working at the particular plant of interest were invited. This design excludes the conclusions to pertain to people outside that population – the external validity or generalisability is low (Rothman 2002). One can argue, though, that external validity exists for people working in the same type of industry if one knows that the exposure is of similar magnitude – it is generalisable to relevant target populations.

At the plant under study, all the workers were invited, and the participation rate at inclusion was 86%. At follow-up, only 20 persons who remained at the plant and who had participated at baseline did not participate in the follow-up. The reasons for not participating were various at both times, but seemed not to depend on lung function or exposure. Therefore, the participants are considered to be representative for the cohort.

A well-known problem regarding occupational studies is the *healthy-hire* and *healthy-worker* effects (Olivieri *et al.* 2010, Arrighi *et al.* 1994). Subjects with respiratory problems are less likely to enter jobs involving inhalation exposures (Olivieri *et al.* 2010). The healthy-worker effect indicates that healthy individuals remain employed and those who experience work-related symptoms leave that job. Symptomatic workers may also avoid exposure situations and/or be more cautious in using personal protection.

Another possible bias is *left-truncation*. This bias occurs when workers hired prior to the start of follow-up (baseline) and still working at baseline are followed up (Applebaum *et al.* 2011). These workers have then already undergone a pre-selection, e.g. through a healthy-hire effect. This is confirmed by the fact that cross-sectional studies have been found to over represent healthier workers (Checkoway *et al.* 2004). Ideally, all workers should have been followed since starting working at the plant. The terms cross-sectional cohort (Weiss 1983) and cross-sectional-follow-up (Koskela *et al.* 1984) have been used to describe a cohort entirely consisting of workers identified at one point in time, i.e. baseline of a study and followed forward. Workers hired before the start of our study may introduce downward bias in exposure-response estimates for null and positive associations. The bias increases with time as the workers who remain at work comprise a larger portion of non-susceptible workers compared to those who have left the work place. Individual changes in lung function during follow-up were studied, and the design is more robust to this type of pre-selection bias. If survivor bias is present here, one would expect it to lead to a smaller lung function decline during follow-up.

Discussion

A more rigorous selection strategy in 2010 excluding those having smoked within 2 hours before the test, might have led to a bias regarding DL_{CO} in the analysis. Because there are some observations included in 2007 of those who had smoked less than 2 hours prior to testing, then a removal of those might lead to a higher expected decline in DL_{CO}. To retain the results from these individuals from 2007 will be conservative; the analysis gives an expected lower rate than the actual fall. It may be an argument for removing these observations if smoke <2 hours before test is considered to affect DL_{CO} significantly. Using the identical criteria in 2007 and 2010 no bias in the analysis was found.

As regards the exposure assessment, a selection bias could be introduced if only some workers accepted to participate, and if those denying participation are, as a group, different from those accepting to participate. All the workers that were requested to participate in the exposure sampling volunteered to do so; hence, a bias in the selection of workers participating in the exposure assessment is not considered.

Information bias

Information bias refers to whether those included in the study are misclassified with respect to outcome or exposure status (Checkoway *et al.* 2004). In this study, the outcome was change in the lung function indices and is not considered to be subject to information bias.

The questionnaires on respiratory symptoms can introduce information bias, as those being ill of chronic obstructive pulmonary disease tend to report more symptoms than those not having disease (Bakke, PS *et al.* 2001). Earlier studies have shown that doctor-diagnosed asthma has a high specificity but low sensitivity (Kongerud *et al.* 1989, Toren *et al.* 1993). A greater sensitivity towards occupational exposure due to the focus on a survey might influence toward an increase in positive replies (Samet 1978). Bakke *et al* comment in their study that exposed subjects might over report respiratory symptoms (Bakke, PS *et al.* 2001). Being three years apart the symptoms may both develop and remit, but the attendants are not likely to recall their former answers and hence bias the results. There seems to be no over-reporting of symptoms.

Exposure misclassification could occur. With the quantitative, group based exposure assessment of randomly selected workers, as chosen in this study, the exposure misclassification is considered to be non-differential (Blair *et al.* 2007).

During the study period the Compound Fertiliser departments and the Calcium Nitrate department were partly reorganised. Few workers were reassigned to other job groups.

Differential misclassification may occur if exposure classification is related to the outcome status. If those with low lung function had been moved to less exposed work, and located to the group “Other” in our study, any true relation between exposed groups and the lung function may be masked. Analysing the lung function in the various job groups, there was no indication of such a bias in the job-group “Other”.

Measurement errors

Measurement errors imply the difference between the estimated group mean decline in lung function and the true group mean decline. This phenomenon can be minimised by increasing the number of subjects, the years of follow-up, or the frequency of measurements (Schlesselman 1973, Berry 1974, Wang *et al.* 2000). Berry used single values of the between- and within-subject variation for different combinations of study duration and measurement frequency to estimate the accuracy of a study (Wang *et al.* 2000, Berry 1974). There were a between-subject standard deviation of 0.539 L/year and a within-subject standard deviation of 0.126 L/year in the data in this study.

Clement and Van De Woestijne argues for a minimum of six to eight years of follow-up to appreciate with precision the rates of decline in lung function in their study among members in the Belgian Air Force (Clement *et al.* 1982). In 2011, the ERS published a task force report; “*Recommendations for epidemiological studies on COPD*” (Bakke, PS *et al.* 2011) aimed at general population studies, but also valuable in the occupational setting. A minimum time of 3 years of follow-up for FEV₁ assessment is recommended, as in this study. Statistically there is no difference in having three measurements compared to two (Schlesselman 1973).

Lung function testing procedures

The spirometer used in this study was the same Vitalograph instrument at both surveys. Also, the same lung diffusing capacity equipment was used throughout the study. The major objective was to follow the change in lung function indices during a three-year period and using the same instruments minimises bias compared to using different instruments.

One criterion for a valid DL_{CO} test is that inspiratory vital capacity (IVC) should be a minimum of 85% of vital capacity. Only two participants had IVC < 85% of FVC, and 131 had IVC > FVC. This finding is contradictory to that found in many population studies (Welle *et al.* 1998, Viegi *et al.* 2001). This result could be due to the study participants in

our study standing when performing the gas diffusion manoeuvre instead of being seated, which is the case in most comparable studies. Also, different instruments may yield different results. Johannessen (Johannessen 2007) compared FVC, FEV₁, and FEV₁/FVC for the Gould spirometer and the Vitalograph spirometer and found that FVC and FEV₁ were lower with the Vitalograph than with the Gould spirometer. Because the manoeuvres were performed with the same instruments at both surveys and the dynamic and diffusing capacity tests were not compared, this factor should not imply any bias.

The same qualified physician instructed the dynamic lung function and diffusing capacity tests at both surveys reducing variance due to several investigators. The quality control and calibration were performed throughout the surveys (Miller *et al.* 2005).

Respiratory symptoms questionnaire

Respiratory symptoms questionnaires have been used extensively throughout the years. In the 1950's the Medical Research Council (MRC) of Great Britain recognized the need for a uniform terminology and methods so that results of prevalence surveys on chronic bronchitis were to be compared and prospective studies could describe accurately the natural history of disease (Samet 1978). The MRC questionnaire on respiratory symptoms was first published in 1960 and has been revised thereafter (British Medical Research Committee 1960). It has been translated into many languages and modified many times. Especially questions being more specific about asthma has been added, like e.g. wheezing (Toren *et al.* 1993).

Validity and reliability are both general problems with questionnaires. Validity refers to the questionnaire's ability to measure which it was designed to measure (Samet 1978, Toren *et al.* 1993). As for validity one also has to understand sensitivity and specificity; sensitivity measures the proportion of true positives correctly identified as positive whereas specificity measures the true negatives as negative. To estimate the validity one needs a "truth/gold-standard". Reliability/repeatability can be tested by having the same individuals answering the questionnaire twice. However, to test this, the questions have to be "hold" questions; i.e. questions where the answer should be the same regardless of the time between the tests. Questionnaire responses can change with time, e.g. long-term changes like in our study, can be caused due to change in illness/symptoms whereas short-term changes are more likely to be due to the variability inherent in answering questionnaires (Brogger *et al.* 2000).

Discussion

In this study, a questionnaire on respiratory illnesses and symptoms including smoking history was used at both occasions of data collection. The majority of the workers had filled in the questionnaires before the lung function testing. After the first round in 2007, it was apparent that the questionnaire was not optimal for our use, although it was a modified validated questionnaire (Kongerud *et al.* 1989) based on the MRC questionnaire (British Medical Research Committee 1960), translated into Norwegian and used before in an industrial setting (Kongerud *et al.* 1990). It turned out that not all the information gathered could be used. As for the questions on respiratory symptoms, the questions on cough and cough with phlegm are not related to any specific time, thereby limiting the knowledge on whether the answer is on acute or chronic symptoms. Time has passed since the validation was conducted and some illnesses are “out of date” and not familiar to everyone, e.g. tuberculosis or lung fibrosis. In addition, one question was particularly misleading to the participants: “*Did you any time, during the last 12 months, experience attacks of breathlessness after completing physical exercising?*” (Personal translation from the applied questionnaire) The ECRHS uses the wording: “*Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?*” First, the question includes two questions; “do you exercise?” and “do you experience attacks of breathlessness after completing physical exercising?” Second, many of the workers exercise regularly and experience breathlessness – on purpose – after the session. Using another questionnaire could have introduced bias because small changes in the phrasing of a question can have effects on prevalence estimates (Brogger *et al.* 2000, Ekerljung *et al.* 2013). The advantages of using the same questionnaire were found to be superior to the disadvantages of using two different questionnaires.

Holland *et al* found that season may influence symptom prevalence, with a higher prevalence in the winter (Holland *et al.* 1969). The examinations were performed at the same time of the year, so this should not influence any change between the two samplings. Nevertheless, the winter of 2010 was colder than the one in 2007, and the employees answered the question on respiratory symptoms in general and not particularly related to working hours. Asthmatic persons can react to cold weather with more symptoms (Hyrkas *et al.* 2014). However, the questionnaire was not designed to study this. The observed increase in morning cough from 2007 to 2010 is difficult to interpret due to the low number of persons reporting the symptom.

Questionnaire on work history

An exposure assessment was conducted during the study period, thus the questionnaire on exposure was not used in our study as a proxy for exposure. The questionnaire included questions on work-related activities during follow-up, possible exposures the workers could have been exposed to previously in their work at the plant, the amount of time spent in exposed areas during the follow-up period, and the use of personal protective equipment (PPE) (Appendix V). The information provided on this questionnaire confirms where the workers were assigned during follow-up and how much time they spent working in the production areas versus the control room. It is known that personal information on the use of PPE can be inadequate. Because of the generally low levels of exposure it was not feasible to further refine the exposure levels, and possible inadequate information on the time spent in the production areas and the use of PPE therefore could not influence the results.

Exposure measurements

A major advantage in this study is the systematic collection of quantitative exposure data with a design to obtain information both on exposure intensity and variability (Heederik *et al.* 2000).

This group based sampling strategy utilizes the fact that Berkson type of error causes little bias (Berkson 1950). The approximate exposure is used for all subjects within the group; and the true exposures, although unknown, may be assumed to vary randomly from this approximate, with mean equal to it (Nieuwenhuijsen 2003).

The analytical measurement error is considered to be small, as well-known methods are used in this study. A systematic error can be introduced if values are consistently too high or too low due to calibration error in the sampling equipment. If this results in an over-estimation of exposure, a decreased risk estimate will be the result, whereas an under-estimation of exposure will give increased risk estimates. There is no reason to believe there were problems with measurement error in the field study as one laboratory trained person had the main responsibility at the plant.

Confounding

Confounding is confusion, or mixing, of effects; the effect of the exposure is mixed together with the effect of another variable, leading to bias (Rothman 2002). If not adequately controlled for in the design or analyses, a confounder may bias the exposure-effect association either farther away or closer to the null than to the true effect. This can be accounted for either by adjustment or stratification. The most important confounders should then be included in the analysis.

Age can be a confounder if it is associated with the exposure under study. That is, if the exposure of interest is time-related, e.g. cumulative exposure or duration of employment, age can be a confounder. The degree and direction of confounding cannot be anticipated when the exposures are not directly related to age, e.g. job group (Consonni *et al.* 1997). Lung function also decreases with age (Fletcher *et al.* 1977). In this study age was adjusted for, and is not considered to have introduced a bias.

Smoking could be a possible confounder as smoking is known to yield a higher prevalence of respiratory symptoms and a larger annual decline in FEV₁ (Kohansal *et al.* 2009). Smoking was adjusted for in the model using self-reported, baseline data for smoking, stratified in three smoking categories (current smoker, ex-smoker, non-smoker). Among those who participated twice, 86% answered identically in 2010 as in 2007 regarding smoking status. Approximately 6% reported to have stopped smoking during the follow-up period. No statistical significant difference in the percentage of the smoking categories in 2007 compared to 2010 was found.

Socioeconomic differences are known to cause differences in health (Eagan *et al.* 2004, Johannessen *et al.* 2010). The causal direction is not clear and suggests the question of whether low social position leads to poor health (social causation) or whether poor health leads to low social position (health selection) (Mæland 2009). The majority of the workers were skilled, had income through the work, and the living conditions were relatively equal and of good standard. Socioeconomic differences are considered to be of little importance in this cohort.

Other risk factors such as genetic factors, particularly α_1 -antitrypsin (Larsson 1978); long-standing asthma (Cassino *et al.* 2000); outdoor air pollution (Gauderman *et al.* 2007, Rojas-Martinez *et al.* 2007); second-hand smoke exposure (Eisner *et al.* 2005, Skogstad *et al.* 2006); and biomass smoke (Caballero *et al.* 2008) are not considered to cause confounding

in our study. Genetically the employees are hypothetically a homogeneous group being predominantly male Norwegians; α_1 -antitrypsin and long-standing asthma were observed, but in such low numbers that it does not have any effect on the results; outdoor air pollution is expected to be identical for those living in the same areas; biomass smoke is primarily outdoors in Norway and as such not a problem here, whereas second-hand smoke exposure could be.

Discussion of the results

Exposure assessment (Paper I)

The exposure assessment strategy for this study was designed to be used in the epidemiological study on possible association between exposure and change in lung function.

Quantitative exposure data was collected for 15 months of the three-year study period. This is important in epidemiological studies because the exposure often varies in time. All workers were eligible for the exposure study and workers who carried personal sampling equipment were selected at random to allow inference concerning exposure level for the entire population and use of proper statistical tools. The goal was to measure each worker for at least two days, however, because the study investigators could not be routinely be on site, the recommendation to sample each person twice was difficult to achieve. Only 23% of the workers had repeated measurements.

New statistical approaches concerning handling of measurements below the limit of detection (LOD) have evolved over the last few years (Hewett *et al.* 2007). A classic approach of analysing datasets that include measurements below LOD is to insert $\text{LOD}/2$ or $\text{LOD}/\sqrt{2}$ for observations below LOD (Hornung *et al.* 1990). Summary statistics are then calculated using these inserted numbers. However, if the proportion of data with measurements below LOD is large this method is not optimal. Instead, we used maximum likelihood estimation (MLE) to compute summary statistics. To perform MLE computations the program uses the numerical values above the limit of detection, information on the proportion of data below the limit of detection, and a mathematical formula for an assumed distribution of the data. Exposure data in this study was shown to be lognormal distributed.

Discussion

An analysis using the observed values (Eduard 2002) was performed and the results were found to be similar (results not shown).

Even though it was not possible to refine the exposure assessment into e.g. cumulative exposure, the group-based strategy still provide valuable information making it possible to divide the workers into similarly exposed job groups. Many studies from similar industries are based upon self-reported information on exposure, job exposure matrix, or stationary sampling.

In epidemiologic studies of the effect of workplace exposures on the frequency and distribution of diseases among groups of workers, it is common to use exposure metrics that do not indicate short-term peak exposure (e.g. cumulative exposure) (Ulvestad *et al.* 2001, Kauffmann *et al.* 1982). However, often the toxicological mechanisms explaining how exposures cause disease are unknown. In such situations, it has been discussed that short-term peak exposures might cause different and more severe effects than the same exposure with lower intensity over a longer time period, because peaks may produce an elevated dose at target organ or overloading repair and protective mechanisms (Nieuwenhuijsen *et al.* 1995, Oberdorster 1995).

In this study, we found that for most agents the time weighted averages were generally low, however, when using PIMEX and direct reading instruments we found that the inhalation exposure profile of these workers consisted of successive exposure peaks resulting from many short term tasks during inspection rounds.

Although self-reported information on what kind of work the person had performed on the day of personal sampling was collected, it was not possible from this information to know which tasks had more exposure or the exact exposure time. The rounds the workers perform include many tasks, and knowing which one to focus on will improve the information on exposure in a study. Other studies have shown that most of the exposure occurs during a short time (Meijster *et al.* 2008, Skaugset 2014). Subsequently, this information could be used to better understand the correlation between exposure and health effects. Although the PIMEX study turned out to have limited scientific value and hence was not published, the information gathered nevertheless was valuable for the company in a preventive perspective.

Lung function (Paper II and III)

Smoking and occupational exposure to dust and fumes are the most important risk factors in developing obstructive pulmonary disease (Fletcher *et al.* 1977, Kohansal *et al.* 2009, Becklake 1985, Blanc *et al.* 2009, Omland *et al.* 2013).

In this longitudinal study of workers at a Norwegian fertiliser plant, an overall statistically significant decline in FEV₁ of 18 mL/yr during the three-year follow-up (Paper II) was found. Other studies from the occupational setting has found an adjusted decline of e.g. 8 mL/yr (Kauffmann *et al.* 1982), 8-10 mL/yr (Hnizdo *et al.* 2003), and 25 mL/yr (Ulvestad *et al.* 2001). Studying each job group, the workers in the nitric acid department had a statistically significant decline in FEV₁ although this group was among the lowest exposed group in the study (Paper II). There was a statistically significant decline in DL_{CO} of 0.068 mmol/min/kPa/year (Paper III). On DL_{CO}, the job group “Other” was the only group with a statistically significant decline. The statistical analyses showed no significant difference in lung function change between the job groups (Paper II and Paper III), and the differences in lung function change for the different job groups must therefore be interpreted with caution.

The longitudinal design in which the subjects serve as their own controls at follow-up is considered as a major strength of this study. The number of participants was acceptable (Berry 1974); the follow-up time of three years is within acceptable limits (Bakke, PS *et al.* 2011); the examinations were performed at the same time of the year, which reduced the effect of seasonal variation known to affect lung function (Senthilselvan *et al.* 2000); and the lung function examinations were performed by one person only using the same equipment, thus reducing the between-worker and within-worker variance.

The linear mixed model corresponds well with known reference values regarding the expected decline due to age, gender and height (discussed later in the statistics paragraph). As for the spirometric values the mixed model estimates about the same values as that of the ECSC reference population regarding FEV₁ and a little above regarding FVC. Quanjer *et al.* uses a population of non-smokers without prior diseases known to affect lung function, but does not exclude on respiratory symptoms (Quanjer *et al.* 1993). In addition, this reference population is derived from several unrelated studies performed between 1960 and 1980 with different standards. Gulsvik *et al.* has a population of asymptomatic people, but includes smokers and ex-smokers (Gulsvik 1979), whereas Langhammer *et al.* only includes asymptomatic, non-smoking people (Langhammer *et al.* 2001). Similarly, the model fits

Discussion

well with the reference values for gas diffusion (Gulsvik *et al.* 1992, Cotes *et al.* 1993). A lower measurement of FEV₁ in an adult cannot be known whether to be due to not having achieved a high maximum during early adulthood, to having a shortened plateau phase, or an accelerated decline, or a combination of these three (Kerstjens *et al.* 1997).

The exposure assessment is both a strength and a limitation in this particular study. Having a quantitative exposure assessment, modelling cumulative exposure with lung function change and refining it with short-term peak episodes might have been possible if the measured concentrations were higher. With many measurements below LOD, job groups were used as a proxy for exposure. The job groups in this study were selected to reflect differences in exposures.

The observed decline in lung function in this study could also be a result of former hazardous exposures having initiated a “vicious circle” including inflammation in the airways (Lapperre *et al.* 2006, Yanbaeva *et al.* 2007). A previous study was performed on the same site as our study and provides some information on earlier exposure (Fandrem *et al.* 1993). The exposure estimates from the period 1966-87 in this particular plant are higher than the present measurements, showing means from the measurements of total dust from 3.2 to 17.8 mg/m³ (Fandrem *et al.* 1993). Since then, the company has built two new factories and the oldest one from that time has closed. Improvements in production equipment occur periodically, and e.g. during the follow-up of this study the company installed a new, enclosed production line in the packing department.

No statistically significant difference in lung function change over 3 years was found when comparing those with employment longer than 25 years to those with employment less than 25 years. The decline in FEV₁ (unadjusted) was not influenced by the number of years worked at the plant (figure 11).

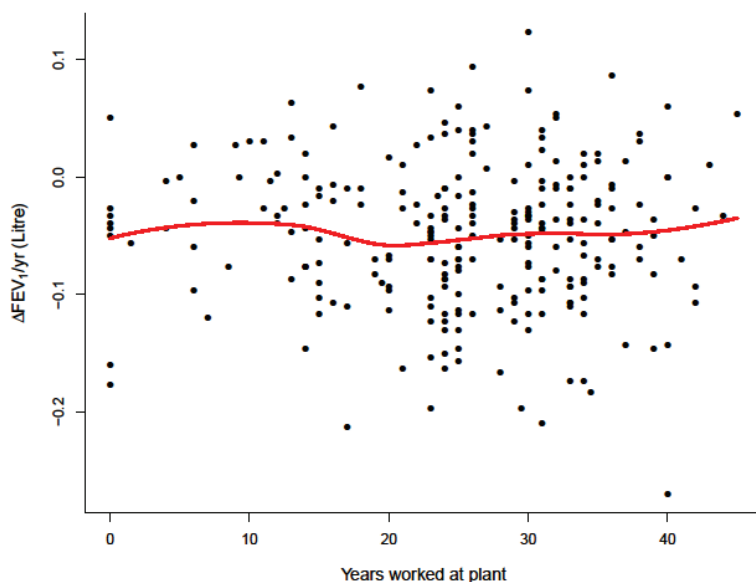


Figure 11. Change in FEV₁ by total years worked at the company

Some workers had accidentally been exposed to high levels of ammonia, nitrous gases or chlorine. An attempt was made to study whether earlier peak exposures could be a cause of an increased risk of lung function decline, but the group had too few cases to analyse.

A large population of ex- and current smokers was included, varying from 52% to 79% depending on the department. It cannot be excluded that the decline in lung function detected in this study could be caused by the effect of smoking, although smoking was adjusted for by inclusion in the model. Sustained pulmonary and systemic inflammation may persist 10-20 years after smoking cessation, thus giving an accelerated decline in FEV₁ in the ex-smokers compared to the non-smokers (Yanbaeva *et al.* 2007, Kohansal *et al.* 2009). However, it is known that smoking cessation is beneficial to lung function (Fletcher *et al.* 1977, Anthonisen *et al.* 2002, Viegi *et al.* 2007, Warnier *et al.* 2013). At the start of the observation period the FEV₁ % predicted was 89% for smokers and 94% for ex-smokers as compared to non-smokers with 99%.

The average age of the men was 47.8 years. The rate of loss in FEV₁ is previously reported to accelerate somewhat with age (Fletcher *et al.* 1977). The relatively high age in our population could contribute to the decrease shown in the present cohort (Ware *et al.* 1990, Ware *et al.* 1996). However, the more elderly workers did not decline faster than the

Discussion

younger, indicating that older age was not an important contributing factor for the group under study.

In this study many exposure measurements were below the limit of detection. The employees were categorised into job groups, but this classification does not take into account the length of the observation period of each worker and differences in exposure levels between agents within and between groups. Looking at the higher exposure for the unloading job compared to the rest of the shipping area, it is opportune to consider whether the groups are appropriate. However, the job-groups are considered representative as the workers rotate among all the tasks in the departments, and therefore are prone to a similarity and frequency of the materials and processes with which they work. The workers seldom swap between departments. There was no information on temporary short-term leave (<1 month) between the first and second lung function testing, which may have led to an overestimation of exposures. Because a substantial number of the measurements of all the agents were below the analytical limit of detection, no quantitative estimates of exposure was used to study the association between exposure and lung function decrease. This factor may have limited the possibility of obtaining optimal grouping of workers in this study. Exposure within job groups can show multi-fold variance, which may lead to misclassification and incorrect conclusions regarding the health - or no health - effects.

All exposure measurements are made outside personal protective equipment (PPE) and the company provides them with PPE as needed for the various exposures. Depending on the work, like whether the exposure is dust or gas, different kind of respirators are used. According to information from many of the workers, the use of PPE has risen the last decades. Most of the time, the workers will know where and when the exposures will occur, and use PPE when mandatory or from their own judgement. In the nitric acid department all the workers have to carry a direct reading device when in the production area. This device will give an alarm whenever the gas concentration is above the Norwegian OEL of 0.6 ppm, and the workers are then to leave the area or use the required PPE. The cranes and dumpers have closed cabins and some also have over-pressure in the cabin. As the exposure estimates were not refined, this will not have lead to any error in our study.

The compound fertiliser departments had the highest median levels of inhalable and thoracic concentrations (Paper I). The thoracic fraction is considered the most relevant for obstructive pulmonary disease (Vincent 2005), but the inhalable fraction gives valuable information on the particle size distribution. In the compound fertiliser departments the

Discussion

mean extrathoracic fraction was 76% indicating that the majority of the aerosol will not reach the tracheobronchial region (European Committee for Standardization (CEN) 1993).

Possible respiratory effects from aerosols may predominantly be related to the water-insoluble aerosol-fraction, and water-solubility was characterised. It was not possible to calculate the partitioning of all the elements in the water-soluble fraction, but if Ca is representative of the water-soluble fraction, approximately one-half of the thoracic mass fraction is water-soluble. This information could not be used in a further refinement of exposure associated lung function decline.

Short-term peak exposure episodes were observed for gases using direct reading instrument, and for dust and gases in the sub study using PIMEX. The association of these short-term peak episodes to lung function changes during follow-up could not be studied as not enough information on the quantity pro person of these episodes were available. Some other studies from the fertiliser industry found reduced lung function and a higher prevalence of reported respiratory symptoms related to ammonia exposure (Ballal *et al.* 1998, Rahman *et al.* 2007). Studies from other settings have shown NO₂ to produce airway obstruction (Bakke, B *et al.* 2001, Brooks *et al.* 1985).

The question of the respiratory risk of short-term peak episodes to aerosols and gases, and long term work at relatively low levels of exposure in this industry thus remains an open one.

Respiratory symptoms questionnaire

Four respiratory symptoms that have been associated with various exposures in occupational settings in Norway (Fell *et al.* 2003, Ulvestad *et al.* 2000, Johnsen *et al.* 2008); cough, cough with phlegm, cough with phlegm > 3 months/year, and wheezing were included in the analyses. One of the studies from Norway encompasses some of the same workers as in this study (Fell *et al.* 2003). The overall prevalence of airway symptoms was lower than in other occupational studies from Norway, and of the four selected symptoms only cough showed a statistical significant change from 2007 to 2010. These symptoms have also been reported in a population study from Norway (Eagan *et al.* 2002). The wording and set-up of the questionnaires differ slightly, and also the prevalence of employees/people reporting symptoms.

Discussion

The prevalence of airway symptoms in this study appears low compared to similar industries (Zuskin *et al.* 2007) or compared to the other occupational settings studied in Norway (Randem *et al.* 2004, Fell *et al.* 2003). This finding was the case at baseline and at follow-up, and no associations were found between the reported symptoms and the change in lung function indices. Kanner *et al* have shown a tendency of respiratory symptoms to be associated with greater declines in FEV₁ (Kanner *et al.* 1999). Fell *et al* found no difference in the prevalence of reported symptoms between controls and exposed workers in the cement producing industry (Fell *et al.* 2003). Regarding wheezing, the prevalence in this study was on the same level as the tunnel workers reported in Ulvestad *et al*'s study (Ulvestad *et al.* 2000), while the prevalence of morning cough and cough during the day were lower than the 30% and 17%, respectively, Ulvestad *et al* found. Laier Johnsen *et al* found a prevalence of 29% for cough and 24.8% for phlegm when coughing, among line operators in the Norwegian smelting industry (Johnsen *et al.* 2008). Reported prevalence of selected respiratory symptoms from some Norwegian studies is shown in table 10.

Table 10. Percentage of selected self reported airway symptoms in various studies from Norway.

	Hovland <i>et al</i> (baseline)	Fell <i>et al</i>	Ulvestad <i>et al</i>	Laier Johnsen <i>et al</i>	Eagan <i>et al</i> (males, baseline)
Wheezing	26.2	46	26	NA	22.0
Morning cough	8.0	32	30	29	23.7
Daily cough with phlegm	10.6	34	NA	NA	11.5
Cough with phlegm > 3 months/yr	6.5	34	NA	24.8	25.0

NA not available

Holland *et al* found that respondents might show a higher prevalence of symptoms when questions were asked in the winter than in the summer (Holland *et al.* 1969). The weather was colder during the follow-up in 2010 than in 2007 and this might contribute to the higher prevalence of cough in 2010 (Hyrkas *et al.* 2014).

In a population study, Jakeways *et al* found that the odds of respiratory symptoms increased with declining levels of all FEV₁ measures, particularly for wheeze and general breathing difficulty (Jakeways *et al.* 2003). Other studies have shown that reported respiratory

symptoms have a low predictive value on the measured results of lung function values (Stahl 2000). Thus, airway symptoms reported among workers must be interpreted with caution.

Rhinometry

The results were analysed and a statistical borderline correlation was found between nasal volume (VOL₂) and FEV₁ percent predicted using the ECSC reference equations (Quanjer *et al.* 1993) but not with the Gulsvik reference equations (Gulsvik 1979, Hovland 2008).

There may be many reasons for a smaller volume in the nose, thus the specificity is low when used in isolation as here.

Rhinometry has previously been used in occupational settings (Ulvestad *et al.* 2001, Heldal *et al.* 2003, Schlunssen *et al.* 2002), and an interaction between the upper and lower airways function has been demonstrated among patients with COPD without using decongestant (Hurst *et al.* 2006). Hellgren *et al.* also studied nasal patency among exposed workers without using decongestant (Hellgren *et al.* 2001) and found no difference between exposed and control groups in the paper industry. Ulvestad *et al.* and Heldal *et al.* studied construction workers and waste handlers, respectively, and found a difference between exposed groups against references (Ulvestad *et al.* 2001, Heldal *et al.* 2003) studying the change in mucosal swelling from the decongestive effect.

Using a decongestant could influence the lung function testing. Introducing a bias by using medication was decided against, as lung function was the major outcome of interest in this study. Thus, rhinometry was not repeated in 2010.

Analysing longitudinal data with a mixed model

A mixed model approach gives several advantages to a more traditional approach that use only complete data with change in lung function as outcome variable and adjust for baseline covariates. The traditional approach avoids the problem with the dependency of repeated measurements as it considers one observation (change in lung function) for each worker. However, this is not without problems; removing individuals with non-complete observations gives potentially more biased estimates as it is less robust to the missing data

Discussion

mechanism. By using mixed model *all* available observations can be exploited whereas removing individuals with non-complete observations results in less power (Fitzmaurice *et al.* 2011).

It is instructive to see how the estimations from the longitudinal mixed model match the reference equations of ECSC (Quanjer *et al.* 1993), Gulsvik (Gulsvik 1979) and Langhammer (Langhammer *et al.* 2001) for the dynamic lung functions, and ECSC (Cotes *et al.* 1993) and Gulsvik (Gulsvik *et al.* 1992) for the diffusing capacity function. As the workers in the study population are predominately males only the reference equations for males are considered, and the mixed model predicted values are for male non-smokers without respiratory symptoms. The linear longitudinal mixed model almost overlaps with the ECSC reference values for FEV₁ as seen in Figure 12, except for the lower age group, as the ECSC assumes constant lung function values for the 18 – 25 age group. The Gulsvik and Langhammer reference equations are clearly above the mixed model predictions, but follow approximately the same declining age trend.

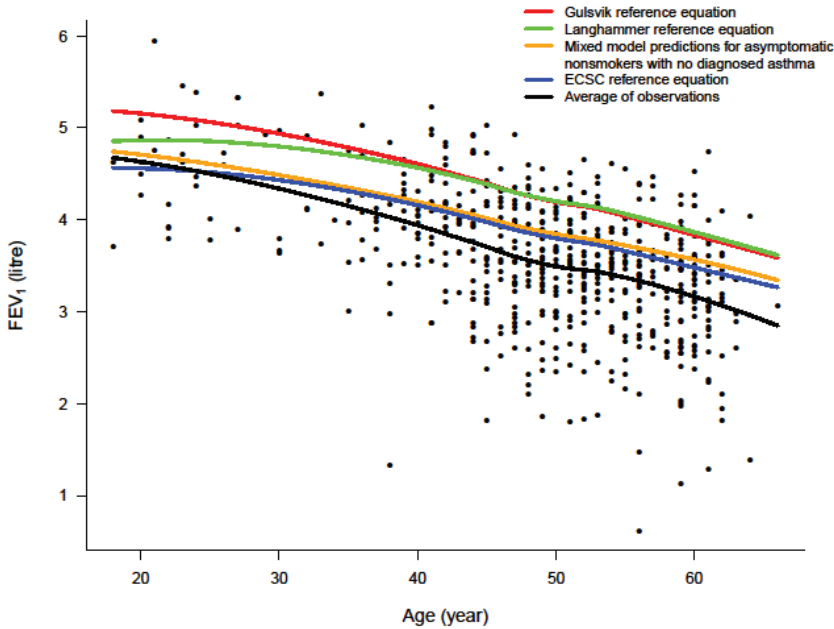


Figure 12. Comparison of reference equations, the mixed model predictions, and the average for all male FEV₁ observations

Discussion

The same tendency is shown for the FVC predicted values. Here, the mixed model predictions are slightly above the ECSC values (figure 13).

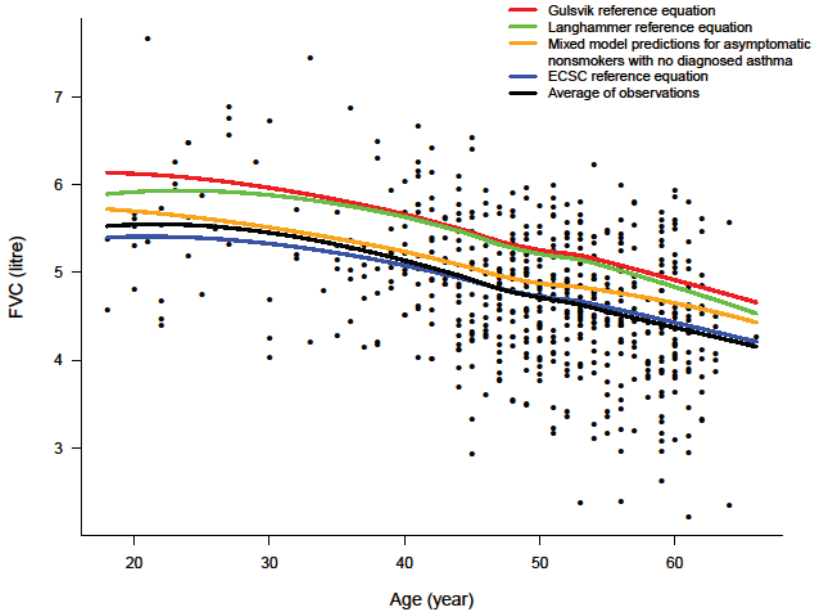


Figure 13. Comparison of reference equations, mixed model predictions, and the average for all male FVC observations

Discussion

Furthermore, for the DL_{CO} values, the mixed model predictions are closest to ECSC; the mixed model predictions cross from being below the ECSC predictions for the ages below 45, to be slightly above after 45 years of age. The expected annual declines were approximately the same as that of Gulsvik's cross-sectional reference population, with -0.056 mmol/min/kPa compared to Gulsvik's -0.057 mmol/min/kPa for men. The ECSC equations yield -0.066 /min/kPa for men (figure 14).

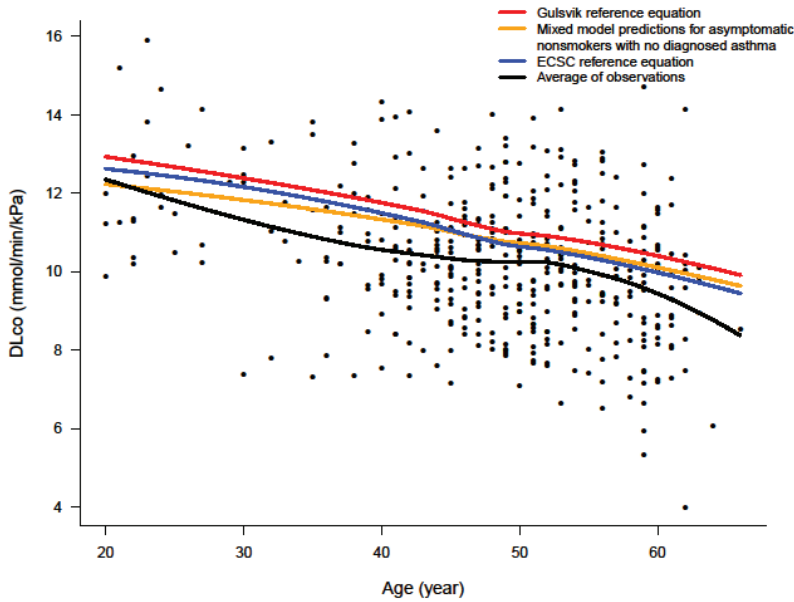


Figure 14. Comparison of reference equations, mixed model predictions, and the average for all male FEV_1 observations

Conclusions & recommendations

Conclusions

In this study of employees at a mineral fertiliser plant a larger than expected decline in lung function indices, both dynamic lung function and lung diffusing capacity, over the three-year follow-up period was found.

The employees were exposed to aerosols and gases, but the overall air concentrations were well below what is considered to cause health risks. The results indicate, though, that the workers may have experienced short-term peak episodes for both aerosols and gases when performing tasks such as e.g. quality control sampling and cleaning.

The prevalence of respiratory symptoms was low compared to other studies from Norway, and only the prevalence of morning cough showed a statistically significant change during follow-up. No association between reported respiratory symptom and the decline in lung function was found among those reporting respiratory symptoms compared to those not reporting respiratory symptoms.

A borderline correlation between rhinometry results and that of dynamic lung function at baseline using the ECSC reference equation was found, however there was no statistically significant correlation using the Gulsvik reference equation.

With the measured exposure levels, no plausible exposure related explanation was found for the overall lung function decline.

Recommendations

The question from Yara when initiating this study was “Is there an increased risk of the employees getting COPD by working here?”

The impression from this particular plant is that the awareness on exposure and possible lung function effects has been high, particularly in the last decade. Furthermore, the reported use of personal protective equipment appears to be adequate. The exposures seem to have declined over the last 20 years and the exposure assessment study provides a good characterisation of the present exposure of aerosols and gases. The focus onward should be on short-term peak exposures.

Ethical considerations

The company and employees were concerned about whether work-related exposure could be a cause of obstructive pulmonary disease, and their concern led to this study. The occupational health service found, in a cross-sectional study, that the percentage of employees with obstructive pulmonary disease was higher in the fertiliser production areas compared to an internal reference group.

In occupational settings, employees may feel an obligation to participate and it is essential to ensure that the participation is voluntary. Written and oral information was given to the employees at the plant about the study. All the participants signed consent forms at both times of the lung function testing. The employees were informed that they could withdraw from the study at any time without stating any reason.

All the employees were invited to participate in the study. The study was approved by the Regional Ethics Committee and by the Norwegian Social Science Data Services (NSD).

All the participants received information on the result of their own lung function test. The physician instructing the subjects would notify the occupational health service if further follow-up was required.

Initially, the right to publish freely the results of the studies was ensured. Yara Norge AS and the Confederation of Norwegian Enterprises (NHO) are gratefully acknowledged for their financial support.

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Appendices

Appendix I	Information form, 2007
Appendix II	Information form, 2010
Appendix III	Consent form, 2007 and 2010
Appendix IV	Health questionnaire, 2007 and 2010
Appendix V	Exposure questionnaire, 2010
Appendix VI	Short overview of the prevalence and incidence of COPD and the development of standardisation
Appendix VII	Short about lung diffusing capacity

Appendix I

Information letter 2007



Statens
arbeidsmiljøinstitutt

UNDERSØKELSE AV LUNGEFUNKSJON

Forespørsel til ansatte ved YARA Porsgrunn.

Som dere kjenner til er det blitt stilt spørsmål om det er en sammenheng mellom eksponering i arbeidsmiljøet deres og nedsatt lungefunksjon. Helseundersøkelser som er foretatt av Herøya Bedriftshelsetjeneste kan tyde på dette.

Yara Porsgrunn ønsker å få avklart om dette medfører riktighet, og har inngått en avtale med Statens arbeidsmiljøinstitutt om en større undersøkelse av dette. En del av denne undersøkelsen er å følge dere som er ansatt ved bedriften, med prøver i forhold til lungefunksjon.

Vi ønsker i denne forbindelsen at du deltar i undersøkelse med spørreskjema, spirometri, TLCO (blåseundersøkelser), og akustisk rhinometri 2 ganger i perioden 2006-2010.

Vi har fått tilgang til navnet ditt gjennom personalavdelingen i bedriften. For at vi skal kunne stole på resultatene vi finner, er det viktig at så mange som mulig deltar i undersøkelsen.

Det er frivillig å delta i undersøkelsen.

Pusteprobe/Spirometri

Er en undersøkelse hvor du skal blåse i et instrument. Det forteller noe om lungefunksjonen din. (samme undersøkelse som bedriftshelsetjenesten gjør)

Blåseundersøkelse - TLCO

Er en undersøkelse hvor en puster inn en bestemt mengde blandingsgass, holder pusten i 10 sek, og deretter blåser det ut. Det viser gassutveksling mellom lunge og blodet.

"Neseromsundersøkelse" - Akustisk rhinometri

Er en undersøkelse hvor det blir holdt et lite instrument, "ekkolodd", foran neseåpningen, som registrerer romforholdene i nesen.

Spørreskjema

I forbindelse med vurdering av forekomst av lungesykdommer er det viktig å få informasjon fra deg om

- Symptomer du evt har fra luftveiene.
- Sykdomshistorie, spesielt med henblikk på hjerte- og lungesykdommer
- Eksponering på arbeidsplass (både nåværende og evt tidligere), og evt fritid.
- Røykevaner

Vi ser at det kan være vanskelig å huske alt, men ber deg svare så godt du kan.

Dersom du ønsker å delta i undersøkelsen ber vi deg om å fylle ut og undertegne vedlagte samtykkeerklæring, og returnere dette sammen med spørreskjemaet til prosjektlege Kristin Hovland samtidig som du kommer til undersøkelse.

Vi vil selvsagt melde fra om eventuelle funn ved undersøkelsen til den enkelte. Ved behov blir du henvist til Bedriftshelsetjenesten for videre oppfølging.

Den informasjonen vi innhenter gjennom undersøkelsene og skjemaet, vil vi samle og analysere. Resultater blir registrert, uten navn, på data for videre bearbeiding. Hvis du ikke motsetter deg det, vil Herøya Bedriftshelsetjeneste få resultatene av undersøkelsene, for oppfølging på et senere tidspunkt. Alle prosjektmedarbeiderne har taushetsplikt.

Vi regner med å avslutte dette prosjektet i 2010. Med tanke på eventuelt å kunne gjøre oppfølging av studien på et senere tidspunkt, ber vi om tillatelse til å lagre dataene for ettertiden (5-10 år), i avidentifisert form. Dataene vil bli avidentifisert like etter at prosjektet er avsluttet i 2010. Det betyr at navn og fødselsnummer ikke lagres sammen med

Appendices

helseopplysningene, men at det vil være mulig ved hjelp av en kodenøkkel å finne tilbake til navn og fødselsnummer dersom innhenting av nye opplysninger skulle bli aktuelt.

Du kan når som helst trekke deg fra prosjektet uten nærmere begrunnelse og uten at det skal få negative konsekvenser.

Prosjektet er tilrådet av Regional etisk komité for medisinsk forskningsetikk og Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste. Det er støttet økonomisk av Yara Porsgrunn.

Hvis du har noen spørsmål er det bare å ta kontakt

Tlf 23 19 51 34

e-post: kristin.hovland@stami.no

Oslo 06

Vennlig hilsen

Statens arbeidsmiljøinstitutt

Knut Skyberg

Overlege, dr.med

Kristin Hovland

Prosjektlege

Appendix II *Information letter 2010*



UNDERSØKELSE AV LUNGEFUNKSJON

Siden 2006 har Yara Porsgrunn i samarbeid med STAMI (Statens arbeidsmiljøinstitutt) og Bedriftshelsetjenesten jobbet med "KOLS-prosjektet" som har til hensikt å undersøke en mulig sammenheng mellom nedsatt lungefunksjon og støv og gasser i vårt arbeidsmiljø.

Nå er prosjektet i en slutfase. Som det ble gitt informasjon om ved forrige lungefunksjonsprøve i 2007, skal den gjentas i 2010 for å se på endringer i denne perioden. Tiden er nå kommet for å gjennomføre denne målingen, med start i januar 2010.

Prosjektet er forankret i Arbeidsmiljøutvalget (AMU). Nye lungefunksjonsprøver (blåseprøver) sammen med et enkelt spørreskjema, vil gi viktig informasjon for å vurdere mulige sammenhenger.

Deltagelse er frivillig, men det er svært viktig for selve undersøkelsen at alle som deltok forrige runde også deltar nå. Det var i alt ca 350 deltakere i 2007.

Selve gjennomføringen av undersøkelsen skjer i regi av STAMI og vil foregå ute i avdelingene.

Pusteprobe/Spirometri

Er en undersøkelse hvor du skal blåse i et instrument. Det forteller noe om lungefunksjonen din. (samme undersøkelse som bedriftshelsetjenesten gjør)

Blåseundersøkelse - TLCO

Er en undersøkelse hvor en puster inn en bestemt mengde blandingsgass, holder pusten i 10 sek, og deretter blåser det ut. Det viser gassutveksling mellom lunge og blodet.

Spørreskjema

I forbindelse med vurdering av forekomst av lungesykdommer er det viktig å få informasjon fra deg om

- Symptomer du eventuelt har fra luftveiene.
- Sykdomshistorie, spesielt med henblikk på hjerte- og lungesykdommer
- Eksponering på arbeidsplass (både nåværende og tidligere), og eventuelt fritid.

Appendices

- Røykevaner

Vi ser at det kan være vanskelig å huske alt, men ber deg svare så godt du kan.

Dersom du ønsker å delta i undersøkelsen ber vi deg om å fylle ut og undertegne vedlagte samtykkeerklæring og returnere dette til prosjektlege Kristin Hovland samtidig som du kommer til undersøkelse. Spørreskjemaet vil bli delt ut før undersøkelsene starter.

Vi vil gi tilbakemelding på undersøkelsen til den enkelte. Ved behov blir du henvist til Bedriftshelsetjenesten for videre oppfølging.

Den informasjonen vi innhenter gjennom undersøkelsene og skjemaet, vil vi samle og analysere. Resultatene blir registrert, i aidentifisert form på data for videre bearbeiding. Alle prosjektmedarbeiderne har taushetsplikt.

Alle opplysninger vil bli behandlet og oppbevart i aidentifisert form etter prosjektets slutt. Det betyr at navn og fødselsnummer ikke lagres sammen med helseopplysningene, men at det vil være mulig ved hjelp av en kodenøkkel å finne tilbake til navn og fødselsnummer dersom innhenting av nye opplysninger skulle bli aktuelt. Vi regner med å avslutte dette prosjektet i 2010. Med tanke på eventuelt å kunne gjøre oppfølging av studien på et senere tidspunkt, ber vi om tillatelse til å lagre dataene i aidentifisert form i ca 7 år. Dersom det ikke blir aktuelt med en oppfølgingsstudie i løpet av denne tidsperioden vil datamaterialet anonymiseres senest 31.12.2017.

Du kan når som helst trekke deg fra prosjektet uten nærmere begrunnelse og uten at det vil få negative konsekvenser i forhold til arbeidsgiver eller bedriftshelsetjeneste.

Prosjektet er tilrådet av Regional komité for medisinsk forskningsetikk og Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste. Det er støttet økonomisk av Yara Porsgrunn.

Hvis du har noen spørsmål er det bare å ta kontakt

Appendices

på telefon 23 19 51 00 eller

e-post: kristin.hovland@stami.no

Oslo januar 2010

Vennlig hilsen

Statens arbeidsmiljøinstitutt

Knut Skyberg

Overlege, dr.med

Kristin Hovland

Prosjektlege

Appendix III *Consent form, 2007 and 2010*



Statens
arbeidsmiljøinstitutt

SAMTYKKESKJEMA

Helseundersøkelse for ansatte ved Yara Porsgrunn

Jeg har mottatt informasjon om prosjektet og er klar over at deltagelse i prosjektet er frivillig og at jeg når som helst kan trekke meg fra prosjektet dersom jeg ønsker det, uten å oppgi grunn.

☐

Jeg samtykker med dette i at følgende opplysninger om meg benyttes i forskningsprosjektet ”Undersøkelse av lungefunksjon hos ansatte ved Yara”, og at disse opplysningene lagres for ettertiden, i aidentifisert form

- Opplysninger fra vedlagte spørreskjema
- Resultater fra undersøkelser som blir utført

☐

Jeg samtykker i at helseopplysningene blir overført til Herøya Bedriftshelsetjeneste.

Navn (blokkbokstaver)

Fødselsnummer (11 siffer)

Underskrift

Dato

Appendix IV Respiratory symptoms questionnaire, 2007 and 2010

<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> SYKDOMMER du har eller har hatt </div> <p>Har du blitt behandlet av lege eller på sykehus for lungebetennelse eller bronkitt?</p> <p style="text-align: right;">Ja Nei</p> <p>Som barn, 0-14 år gammel <input type="checkbox"/> <input type="checkbox"/></p> <p>Som ungdom, 15-20 år gammel <input type="checkbox"/> <input type="checkbox"/></p> <p>Som voksen <input type="checkbox"/> <input type="checkbox"/></p> <p>Har du blitt behandlet av lege eller på sykehus for noen av de følgende sykdommene?</p> <p style="text-align: right;">Kryss av</p> <p>Øyeallergi, neseallergi eller hørsnue <input type="checkbox"/></p> <p>Eksem, inkludert barneeksem <input type="checkbox"/></p> <p>Tuberkulose <input type="checkbox"/></p> <p>Pleuritt <input type="checkbox"/></p> <p>Sarkoidose <input type="checkbox"/></p> <p>Støvlungesykdom, f.eks. silikose, asbestose <input type="checkbox"/></p> <p>Lungefibrose <input type="checkbox"/></p> <p>Emfysem el.KOLS (kronisk obstruktiv lungesykdom) <input type="checkbox"/></p> <p>Koronar hjertesykdom (hjerteinfarkt eller angina) <input type="checkbox"/></p> <p>Andre hjertesykdommer, i så fall oppgi hvilke: <input type="checkbox"/></p>	<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> Navn Dato </div> <div style="border: 1px solid black; padding: 5px;"> SYMPTOMER FRA LUFTVEIENE, nåværende og tidligere </div> <p style="text-align: right;">Ja Nei</p> <p>Har du hatt hvesing eller piping i brystet på noe tidspunkt i løpet av de siste 12 månedene? <input type="checkbox"/> <input type="checkbox"/></p> <p>Har du blitt vekket av en følelse av å være tett i brystet om morgenen i løpet av de siste 12 månedene? <input type="checkbox"/> <input type="checkbox"/></p> <p>Har du på noe tidspunkt i løpet av de siste 12 månedene hatt anfall av tungpustenhet i løpet av dagen uten at du hadde anstrengt deg? <input type="checkbox"/> <input type="checkbox"/></p> <p>Har du på noe tidspunkt i løpet av de siste 12 månedene hatt anfall av tungpustenhet som kom etter at du hadde gjennomført fysisk trening? <input type="checkbox"/> <input type="checkbox"/></p> <p>Har du på noe tidspunkt i løpet av de siste 12 månedene blitt vekket om natten av et anfall av tungpustenhet? <input type="checkbox"/> <input type="checkbox"/></p> <p>Har du på noe tidspunkt i løpet av de siste 12 månedene blitt vekket om natten av et hosteanfall? <input type="checkbox"/> <input type="checkbox"/></p> <p>Hoster du som regel når du våkner om morgenen? <input type="checkbox"/> <input type="checkbox"/></p> <p>Hoster du som regel opp slim fra lungene (oppspytt) når du våkner om morgenen? <input type="checkbox"/> <input type="checkbox"/></p> <p>Har du hostet opp slim fra lungene (oppspytt) de fleste morgenerne minst tre måneder hvert år? <input type="checkbox"/> <input type="checkbox"/></p> <p>Hvilket av de følgende utsagn beskriver din pust best?</p> <p>a) Jeg har aldri / svært sjelden problemer med pusten <input type="checkbox"/> <input type="checkbox"/></p> <p>b) Jeg får regelmessig problemer med pusten, men det blir alltid fullstendig bra igjen etterpå <input type="checkbox"/> <input type="checkbox"/></p> <p>c) Min pust er aldri helt bra <input type="checkbox"/> <input type="checkbox"/></p> <p>Når du er i støvete deler av huset eller sammen med dyr (f.eks. hunder, katter eller hester) eller i nærheten av fjær (f.eks. puter, dyner, edderdun), opplever du noen gang:</p> <p>a) Å få en følelse av å være tett i brystet? <input type="checkbox"/> <input type="checkbox"/></p> <p>b) Å bli tungpusten? <input type="checkbox"/> <input type="checkbox"/></p>	
<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> ALLERGI </div> <p style="text-align: right;">Ja Nei</p> <p>Har du noen gang hatt allergi mot f.eks. gress, dyr? <input type="checkbox"/> <input type="checkbox"/></p> <p>Hvis ja, oppgi hvilken type allergi:</p> <p style="text-align: right;">Kryss av</p> <p>Symptomer fra øynene, renning <input type="checkbox"/></p> <p>Symptomer fra nesen, nysing, rennende eller tett nese <input type="checkbox"/></p> <p>Astma <input type="checkbox"/></p> <p>Hudsymptomer, eksem, eller kløende utslett <input type="checkbox"/></p> <p style="text-align: right;">Ja Nei</p> <p>Har en lege bekreftet din allergidiagnose? <input type="checkbox"/> <input type="checkbox"/></p> <p style="text-align: right;">Ja Nei</p> <p>Har noen i din familie noen gang hatt allergi? <input type="checkbox"/> <input type="checkbox"/></p> <p>Mor, far eller søsken <input type="checkbox"/> <input type="checkbox"/></p> <p>Barn <input type="checkbox"/> <input type="checkbox"/></p> <p>Ektefelle <input type="checkbox"/> <input type="checkbox"/></p>	<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> ASTMA </div> <p style="text-align: right;">Ja Nei</p> <p>Har du noen gang hatt astma? <input type="checkbox"/> <input type="checkbox"/></p> <p>Hvis "ja",</p> <p style="text-align: right;">Kryss av</p> <p>-Ja, som barn eller ungdom <input type="checkbox"/></p> <p>-Ja, som voksen <input type="checkbox"/></p> <p>-Ja, fremdeles / nå <input type="checkbox"/></p> <p style="text-align: right;">Ja Nei</p> <p>Har du hatt astmaanfall i løpet av de siste 12 månedene? <input type="checkbox"/> <input type="checkbox"/></p> <p>Tar du medisiner mot astma (inkl. inhalatorer, aerosoler og tabletter)? <input type="checkbox"/> <input type="checkbox"/></p> <p>Startet din astma (første gang) i løpet av de siste ti årene? <input type="checkbox"/> <input type="checkbox"/></p> <p>Har en lege bekreftet din astmadiagnose? <input type="checkbox"/> <input type="checkbox"/></p> <p style="text-align: right;">Ja Nei</p> <p>Har noen i din familie noen gang hatt astma: <input type="checkbox"/> <input type="checkbox"/></p> <p style="text-align: right;">Kryss av</p> <p>Mor, far eller søsken? <input type="checkbox"/> <input type="checkbox"/></p> <p>Barn? <input type="checkbox"/> <input type="checkbox"/></p> <p>Ektefelle? <input type="checkbox"/> <input type="checkbox"/></p>	<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> RØYKING </div> <p style="text-align: right;">Ja Nei</p> <p>Røyker du nå (siste måned)? <input type="checkbox"/> <input type="checkbox"/></p> <p>Hvis du ikke røyker daglig nå, har du noen gang røykt minst en sigarett pr. dag i et helt år? <input type="checkbox"/> <input type="checkbox"/></p> <p>Hvis du har røykt tidligere, men ikke røyker nå: Kryss av</p> <p>Sluttet du å røyke for mindre enn et år siden? <input type="checkbox"/></p> <p>Sluttet du å røyke for et år siden eller mer? <input type="checkbox"/></p> <p>Hvis du røyker eller har røykt tidligere: år</p> <p>Hvor gammel var du da du begynte å røyke? Alder: <input type="text"/> <input type="text"/></p> <p>Hvor mange år har du røykt til sammen? Antall år: <input type="text"/> <input type="text"/></p> <p>Hvor mye røyker/røykte du i gj. snitt? Antall</p> <p>(antall sigaretter per dag) <input type="text"/> <input type="text"/></p>

Appendix V

Work exposure questionnaire, 2010

Navn:

Fabrikk og skift:

1. Har du hatt de samme arbeidsoppgaver/jobbet ved samme fabrikk siste 3 år Ja Nei
(siden forrige lungeundersøkelse)?

Hvis nei, kan du skrive hvor du har jobbet? (inkludert arbeid utenfor
Yara/permisjon/langvarig sykdom eller lignende)

Tidsrom Arbeidssted

2. Vennligst skriv ned alle jobbene du har hatt etter vanlig skolegang. (med varighet mer
enn 1 år)
(For arbeid ved Hydro/Yara vennligst skriv hvilke fabrikker, hvis du har jobbet ved
flere over lengre perioder)

Tidsrom Bedrift Stilling/yrke

3. Har du noen gang arbeidet med/vært eksponert for følgende i 1 år eller mer?

- | | | | |
|-------------------------------------|----|----------|-----|
| a) Asbest | Ja | Vet ikke | Nei |
| b) Kvarts | Ja | Vet ikke | Nei |
| c) Jordbruksproduksjon (bondeyrket) | Ja | Vet ikke | Nei |
| d) Sveising og platearbeid | Ja | Vet ikke | Nei |
| e) Isocyanater | Ja | Vet ikke | Nei |

Appendices

4. Har du noen gang vært til lege/sykehus pga akutt gass forgiftning?
- | | | |
|--------------|----|-----|
| a) Nitrose | Ja | Nei |
| b) Ammoniakk | Ja | Nei |
| c) Klor | Ja | Nei |
| d) Annet | Ja | Nei |

I tilfelle når?

5. Har du regelmessig fritidsaktivitet(er) som gir støv- eller gassforurensning av innåndingsluften?
- | | | |
|--|----|-----|
| | Ja | Nei |
|--|----|-----|

Hvis ja, hva slags aktivitet?

6. Hvor mange dager per uke/skiftperiode jobber du bare i kontrollrommet?
-dager/uke/periode

7. Roterer du på de forskjellige utejobbene?
- | | | |
|--|----|-----|
| | Ja | Nei |
|--|----|-----|

Hvis nei, hvilke jobber går du på?

8. Bruker du støvmaske/åndedrettsvern når det er pålagt?
- | | | | |
|--------|------|-----------|-------|
| Alltid | Ofte | Av og til | Aldri |
|--------|------|-----------|-------|

9. Har du endret røykevaner siste 3 år?
- | | | |
|--|----|-----|
| | Ja | Nei |
|--|----|-----|

Hvis ja, hvordan? (f.eks økt/reduisert antall sigaretter, sluttet, begynt igjen)

Takk for at du tok deg tid til å svare på spørsmålene!

Appendix VI *Short overview of prevalence and incidence of COPD and the development of standardisation*

Pulmonary obstruction

A short overview of the prevalence and incidence of COPD and the development of standardisation is included because the concern about a higher prevalence of COPD among the employees at the fertiliser production plant initiated this study.

Prevalence/incidence

COPD is expected by the WHO to be the third most common cause of mortality by 2020 (<http://www.who.int/respiratory/copd/burden/en/index.html>), yet most national data show that less than 6% of the adult population has been told about having COPD (Vestbo *et al.* 2012). In Norway, two studies show a prevalence of COPD of 4.1% and 4.5% (Bakke, PS *et al.* 1991, Gulsvik, A. 1979). This percentage most likely reflects under-recognition and under-diagnosis of COPD. In another study from Norway, Johannessen *et al.* estimated that only about one-half of those with COPD are diagnosed (Johannessen *et al.* 2005). The same trend is found in Sweden (Lindberg *et al.* 2006). The cumulative incidence of the GOLD-defined chronic obstructive pulmonary disease in a general adult population in Western Norway was 6.1% (Johannessen *et al.* 2005). Lindberg *et al.* found a ten-year cumulative incidence in Northern Sweden of 8.2% (using BTS criteria) and 13.5% (using GOLD criteria) (Lindberg *et al.* 2005).

Pulmonary obstruction is preferably diagnosed with spirometry test. Earlier this diagnostic procedure was a suggestion in the GOLD criteria, but it is now a requirement in the latest GOLD update (Vestbo *et al.* 2012). Globally this criterion is not practicable, and the diagnosis must be made on symptoms only. In epidemiological studies respiratory symptoms have been used as criteria for obstructive disease (Heederik *et al.* 1990, Lundback *et al.* 1994, Gulsvik, A. 1979). Spirometry is a crucial test, however, and has been applied in epidemiological studies (Johnsen *et al.* 2008, Ulvestad *et al.* 2000) and in the clinic for years. Because the definition on obstructive abnormality has varied over the continents and through the years (Vestbo *et al.* 2012, Quanjer *et al.* 1993, 1997), it is difficult to assess the burden of obstructive disease in the population (Lindberg *et al.* 2005).

Standardisation

Regarding questionnaires on respiratory symptoms the British Medical Research Council published the first standardised questionnaire in 1960 (British Medical Research Committee 1960). This questionnaire was developed in a setting where smoking and use of coal/mining (the London Smog) caused chronic obstructive disease. Thus, the questionnaire had only a few questions on wheezing (British Medical Research Committee 1960, Toren *et al.* 1993). The following questionnaires included more questions on asthma such as American Thoracic Society's questionnaire of 1978 (Alavanja *et al.*) and the International Union Against Tuberculosis and Lung Diseases (IUATLD) in the 1980s (Burney, P *et al.* 1987). In Norway, Kongerud *et al* validated a translated, modified MRC questionnaire (Kongerud *et al.* 1989). The ECRHS used several pre-existing questionnaires to develop the questionnaire for their survey (Burney, PG *et al.* 1994).

With this discussion on terminology and the development of questionnaires, there emerged a standardisation for pulmonary function testing. ATS published a document on "Standardization of Spirometry" in 1979 (1979), including subsequent updates. The ECSC/ERS published their statements from 1983 onward (1983). In 2005, ATS and ERS published a joint statement, which is currently in use (Miller *et al.* 2005).

Criteria

In the late 1990s, a committed group of scientists wanted to bring more attention to the prevention and management of COPD and, on behalf of the US Heart, Lung, and Blood Institute (the NHLBI) and the WHO, founded the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The first consensus report was available in 2001 (Pauwels *et al.* 2001), with the last update in 2011 (Vestbo *et al.* 2012). The GOLD document of 2011 states that: "*Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.*" The primary mechanisms underlying airflow limitations in COPD are: small airway disease, airway inflammation, airway fibrosis, luminal plugs, and increased airway resistance on one hand, and parenchymal destruction, loss of alveolar attachments, and decrease of elastic recoil on the other hand.

Appendices

The document states that any person with dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease and age above 40 should be considered for COPD. The spirometry test, including post-bronchodilator spirometry, is required for the diagnosis according to GOLD. Airflow limitation without concordant symptoms is possible. Cellular and molecular indices are not yet mandatory for the diagnosis. The recommendation states that screening for α 1-antitrypsin (AAT) deficiency should be performed in COPD patients from high prevalence areas and young (<45 years) COPD patients.

GOLD is effective with a clinical diagnosis and maintains the post-bronchodilator ratio of $FEV_1/FVC < 0.7$ with four grades of the degree (mild, moderate, severe, and very severe) of airflow limitation as before (split at 80%, 50% and 30% of predicted value). In addition, the GOLD criteria recommend the assessment of symptoms, lung function, risk of exacerbations and comorbidities.

The current ATS/ERS guideline requires post-bronchodilator spirometry test for the diagnosis (Celli *et al.* 2004). The ATS/ERS have spirometric classification equal with that of GOLD, except the stadium “At risk” with $FEV_1/FVC < 0.7$ and FEV_1 % predicted ≥ 80 . At risk is defined as; “*patients who smoke or have exposure to pollutants, have cough, sputum or dyspnoea*” (Celli *et al.* 2004).

There is an ongoing discussion of whether the FEV_1/FVC ratio < 0.7 or Lower Limit of Normal (LLN) should be used in diagnosing airflow obstruction. Lower Limit of Normal refers to the statistically lower fifth percent of a reference population and is calculated by subtracting 1.64 times the standard deviation (SD) from the mean. It has been shown that a fixed ratio under-estimates the diagnosis among the young (Cerveri *et al.* 2008) and over-estimates the diagnosis among the elderly (Hardie *et al.* 2002). For epidemiological studies on COPD, ERS published a task force report in 2011 (Bakke, PS *et al.* 2011) that recommends using the LLN (post-bronchodilatory) to define COPD. Swanney *et al* (Swanney *et al.* 2008) claim that using the LLN rather than the FEV_1/FVC ratio reduces the misclassification of airway obstruction. In the article by Swanney *et al*, a figure showing the reference values for the LLN range from 57 studies is shown, and these data indicate the importance of selecting the right reference population. There are few, if not only one, reference equation based on post-bronchodilatory values (Johannessen *et al.* 2006).

Appendix VII Lung diffusing capacity

Although spirometry test is the “gold standard” for examining lung function, diffusing capacity is widely used as a supplement in clinical medicine. It has been used in population based and in occupational epidemiological studies (Nogueira *et al.* 2011, Welle *et al.* 1999). The single-breath determination of carbon-monoxide uptake in the lung (DL_{CO}) was first described by Marie Krogh in 1915 (Krogh). The term “transfer factor for carbon monoxide” (TL_{CO}), expressed as mmol/min/kPa (SI unit), is primarily used by the European community, whereas North Americans use “lung diffusing capacity for carbon monoxide” (DL_{CO}), expressed as mL/min/mmHg (the conversion factor is “ TL_{CO} ”(SI unit) = “ DL_{CO} ”/2.896). The joint ATS/ERS standardisation as of 2005 (MacIntyre *et al.* 2005) uses DL_{CO} . It is a product of the CO uptake from the lung (K_{CO} – carbon monoxide transfer coefficient) and the alveolar volume, V_A , where K_{CO} is measured as a concentration fall in alveolar CO per unit time per unit CO driving pressure ($P_{A,CO}$): $K_{CO} = \Delta[CO]/\Delta t / P_{A,CO}$ and V_A is the volume of gas in the lung containing CO. $V_A = IVC \times (\text{He inspired concentration} / \text{alveolar sample He gas concentration})$.

The term “diffusion capacity” is commonly used, but does not fully reflect that it is a conductance and that CO uptake involves passive diffusion over the alveolar and red cell membrane, and chemical binding with haemoglobin (Hb).

CO uptake can be simplified into two conductance properties (in series) as follows: membrane conductivity (D_M) and the binding of CO and Hb. D_M reflect the diffusion properties of the alveolar capillary membrane and the erythrocyte membrane. The binding of CO-Hb can be represented as θVc ; θ is the rate with which CO combine with intracellular Hb in 1 mL of blood expressed as mL CO/min/mmHg while Vc is the volume of Hb in alveolar capillary blood (the volume of capillary bed available for gas exchange (in mL), independent of the packed cell volume).

$$\frac{1}{DL_{CO}} = \frac{1}{D_M} + \frac{1}{\theta Vc}$$

Physiologic changes in D_M or θVc thereby influence DL_{CO} .

